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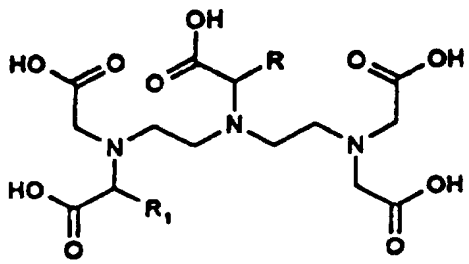
(54) Title: DIAGNOSTIC IMAGING CONTRAST AGENT WITH IMPROVED IN-SERUM-RELAXIVITY

(57) Abstract



(I)

Compounds of formula (I), both in the racemic and optically active forms in which R is H, or a linear or branched, saturated or unsaturated C_1-C_{20} alkyl, optionally interrupted by one or more -CH(OH)-, -CONH-, -NHCO-, -CO-, -CH(NH_2)-, -SO-, -SO_2-, SO_2NH- groups and/or one or more N, O, S atoms optionally substituted with one or more -COOH groups and/or amide or ester derivatives thereof, and in which said alkyl chain is interrupted or substituted by at least 2, which are independently the same or different, isolated or fused, cyclic L residues, with the proviso that, when some L residues are fused together, the resulting polycyclic unit comprises no more than 3 cyclic group, and in which L is a carbocyclic or heterocyclic, saturated or unsaturated or aromatic cyclic unit, comprising from 5 to 6 atoms, optionally substituted by one or more X groups, which are independently the same or different, in which X is OH, halogen, NH_2, NHZ, $N(Z)_2$, -OZ-, -SZ-, COZ, where the Z groups can independently be a C_1-C_5 linear or branched alkyl, optionally substituted with one or more -OH, -COOH or alkoxy groups, or said X group is a -COOH group or a derivative thereof, such as an ester or an amido group, or -SOZH group or an amino derivative of the same; R_1 is the same as R with the provisos that: R and R_1 cannot be at the same time H; when R is different from H, R_1 is H; when R_1 is different from H, R is H; as well as the complexes of the compounds of fomula (I) with metal ions of atomic number from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83 and the salts thereof with physiologically acceptable organic bases selected from primary, secondary or tertiary amines, or basic amino acids, or with inorganic bases the cations of which are sodium, potassium, magnesium, calcium or the mixtures thereof. Said compounds are useful as contrast agents in Magnetic Resonance Imaging and have improved relaxivitty in human serum.

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DIAGNOSTIC IMAGING CONTRAST AGENT WITH IMPROVED IN-SERUM-RELAXIVITY

Technical field of the invention

This invention relates to the Magnetic Resonance Imaging (M.R.I.), a technique used in the medical diagnosis field for a number of years, to rapidly detect a series of anomalies and/or pathological conditions of living human or animal body organs or tissues. (i. e.: Stark D.D., Bradley W.G. Jr., Eds. : "Magnetic Resonance Imaging", the C.V. Mosby Company, St. Louis, Missouri (USA), 1988). In particular, the invention relates to new chelating agents, especially aminopolycarboxylic acid derivative compounds and to metal chelates thereof with bivalent or trivalent paramagnetic ions and/or salts thereof as well as their use as M.R.I. contrast agents.

Background of the invention

Diagnostic imaging techniques, such as Magnetic Resonance Imaging. have been used in medical diagnosis for a long time. The use of contrast media to improve tissue differentiation, to delineate structures or monitor physiological functions constitutes in some cases a fundamental contribution in the best formulation of some medical diagnosis and a valid support for radiologist work.

The medical use of aminopolycarboxylic acid or carboxylic acid derivatives and metal chelates thereof as M.R.I. contrast agents is well known. Said contrast agents, to simplify, can be seen as pertaining to two main groups: the linear and the cyclic ones.

The present invention relates to linear polyaminopolycarboxylic acid derivatives, as well as their complexes with paramagnetic metal ions, in particular the Gd^{3+} ion.

Patent literature is rich in patent and patent applications relating to the use of linear polyaminopolycarboxylic acid derivatives in the preparation of MRI contrast agents. These compounds generally are derived from the simplest one, N,N,N',N'',N''-diethylenetriamine-pentaacetic acid, (DTPA), of which the Meglumine salt of the Gd^{3+} complex has been commercialised for a number of years as MAGNEVIST(R). To improve stability, water solubility and selectivity and to reduce toxicity of these contrast agents generally patent literature proposes the preparation of esters or amido derivatives of said acids or the introduction of substituents on the diethylene unit of the diethylenetriamine DTPA skeleton. As an example of said patent literature we can cite: Guerbet EP 661279; Concat Ltd., WO 95/05118; Dibra WO 95/15319; Mallinckrodt WO 94/08630; Green Gross Corp. JP 06016606 and JP 05229998; Mallinckrodt US 5,141,740 and US 5,077,037; Cockbain-Nycomed WO 91/15467 and WO 92/11232; Salutar US 4,889,931 and 4,858,451; Abbot Laboratoires EP 279307; Nycomed EP 299795; Metasyn Inc. WO 95/28179; Schering EP 680 464; and document cited in these patent publications. Some documents further exist in which substituents have been introduced in α to one or more carboxylic DTPA groups; for example: Bracco EP-B-230893 and US 5,182,370; Schering WO 96/16928, WO 96/16929, WO 96/26180 and DE 4341724 enclosing α derivatives,

generally comprising an aromatic group, particularly useful for the imaging of the hepatobiliary system. In particular, some patent literature further exist, in which the introduction of an aromatic or lipophilic group on the chelant structure is specifically stated to make the contrast agent particularly useful for a best definition of the liver and the biliary duct: the General Hospital Corporation US 4,899,755 and WO -A-86/06605.

Summary of the invention

The compounds of the present invention are diethylenetriaminepentaacetic acid derivatives characterised by having a hindering group in α to at least one of the 5 DTPA carboxylic groups wherein said substituent has the dimension of a C_1-C_{20} alkyl, linear or branched, saturated or unsaturated chain, which is substituted or interrupted by at least two cyclic, optionally aromatic, carbocyclic or eterocyclic, saturated or unsaturated, isolated or fused units.

Said hindering group is probably responsible for the interaction of the paramagnetic chelates with biological components of the fluids in which the agent diffuses, wherein said interaction produces the surprisingly high relaxivity values that we have measured in Human Reconstructed Serum.

Relaxivity values of the contrast agent of the present invention have been tested either in saline or in human serum obtained by Seronorm™ Human, freeze-dried human serum produced by Nycomed Pharma AS, Oslo, Norway. Serum obtained from said Seronorm™ is substantially equivalent to the fresh one, so its use in

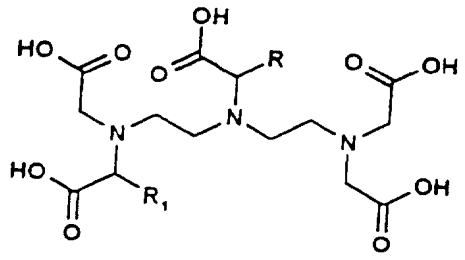
the relaxivity determination grants a good picture of the "in vivo" behaviour and, further, an excellent reproducibility of this test.

The compounds object of the present invention are characterised by very high r_1 and r_2 relaxivity values. When measured in Seronorm™ Human at 20 MHz, at a temperature of 39°C, and at a concentration comprised from 0 to 1 mM, compounds of the present invention usually have r_1 relaxivity equal to or, preferably, higher than 15 $s^{-1}mM^{-1}$.

Detailed disclosure of the invention

The present invention relates to novel chelating agents, more particularly linear aminopolycarboxylic acid derivatives chelants, and metal chelates thereof and the use of such chelating agents and chelates in the preparation of diagnostic imaging contrast agents and in particular of contrast agents exhibiting improved serum relaxivity.

Said compounds are polyaminopolycarboxylic acid derivatives of formula (I)



(I)

in which :

R is H, or a linear or branched, saturated or unsaturated C_1-C_{20} alkyl, optionally interrupted by one or more -CH(OH)-, -CONH-, -NHCO-, -CO-,

$-CH(NH_2)-$, $-SO-$, $-SO_2-$, SO_2NH- groups and/or one or more N, O, S atoms, optionally substituted with one or more -COOH groups and/or amide or ester derivatives thereof, and in which said alkyl chain is interrupted or substituted by at least 2, which are independently the same or different, isolated or fused, cyclic L residues, with the proviso that, when some L residues are fused together, the resulting polycyclic unit comprises no more than 3 cyclic group, and in which

L is a carbocyclic or heterocyclic, saturated or unsaturated or aromatic cyclic unit, comprising from 5 to 6 atoms, optionally substituted by one or more X groups, which are independently the same or different, in which

X is OH, halogen, NH_2, NHZ, $N(Z)_2$, -OZ- , -SZ, -COZ, where the Z groups can independently be a C_1-C_5 linear or branched alkyl, optionally substituted with one or more -OH, -COOH or alkoxy groups,

or said X group is a -COOH group or a derivative thereof, such as an ester or an amido group, or an -SOZH group or an amido derivative of the same;

R_1 is the same as R with the provisos that:

R and R_1 cannot be at the same time H;

when R is different from H, R_1 is H;

when R_1 is different from H, R is H.

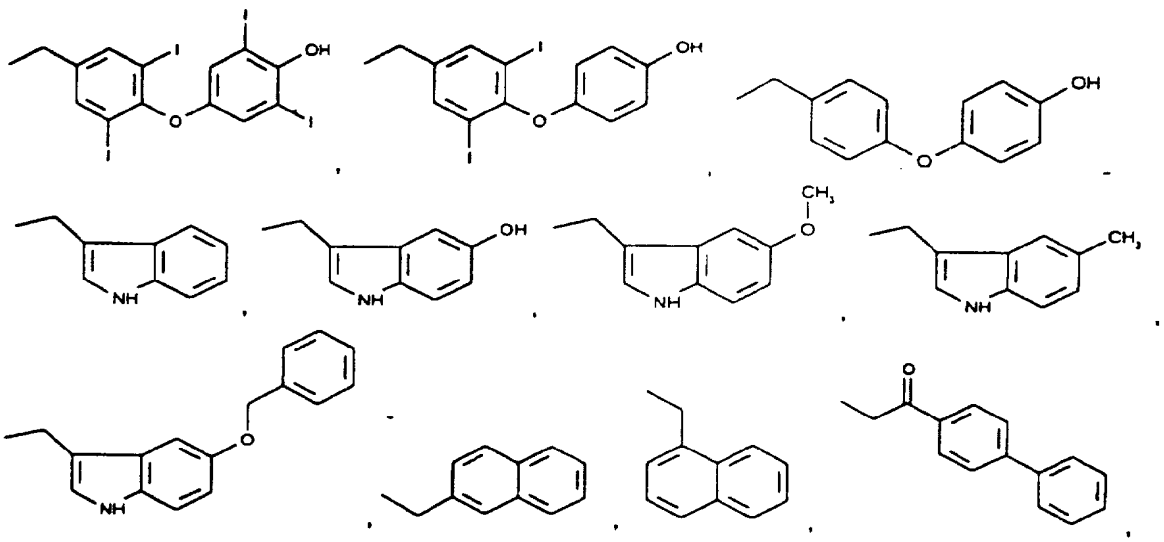
The compounds comprised within formula (I) can be either racemic or optically active.

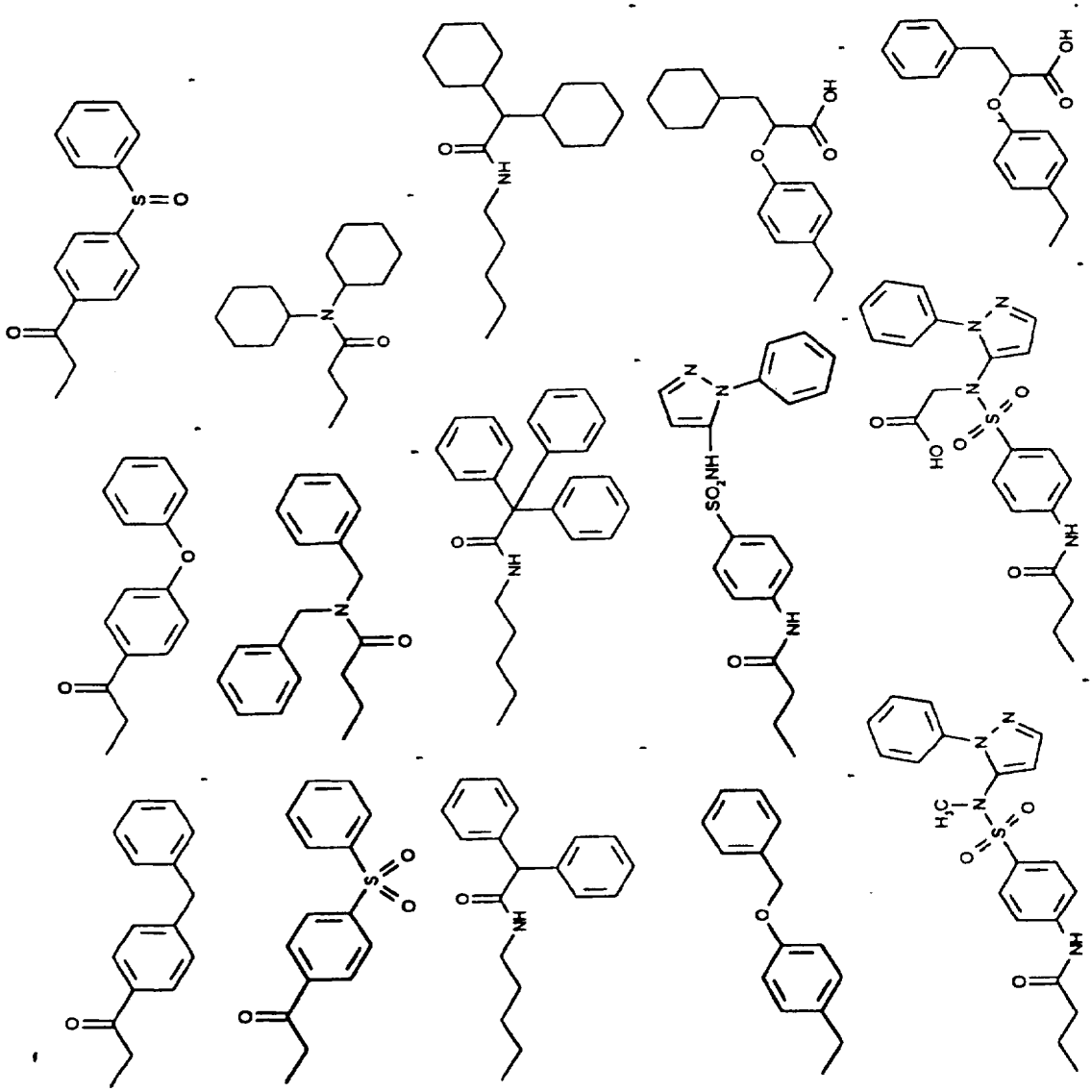
The invention further comprises complexes of the ligand of formula (I) with metal ions of atomic number from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83;

particularly preferred metals being: $Fe^{(2+)}$, $Fe^{(3+)}$, $Cu^{(2+)}$, $Cr^{(3+)}$, $Gd^{(3+)}$, $Eu^{(3+)}$, $Dy^{(3+)}$, $La^{(3+)}$, $Yb^{(3+)}$, $Mn^{(2+)}$; as well as, where the metal chelate carries an overall charge, a salts thereof with a physiologically acceptable counterion, preferably selected from organic bases such as a primary, secondary or tertiary amines, a basic amino acid, or an inorganic base derived from an alkali metal or alkaline-earth metal cation such as: Na^+, K^+, Mg^{2+}, Ca^{2+} or a mixture thereof.

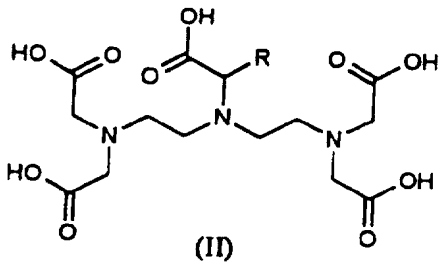
The present invention further relates to the use of the compounds of formula (I) and of the salts of the complexes thereof as well as the pharmaceutical formulations containing them for a diagnostic or therapeutic scope.

Preferred are the compounds of formula (I) in which R or R_1 are selected from the following groups:





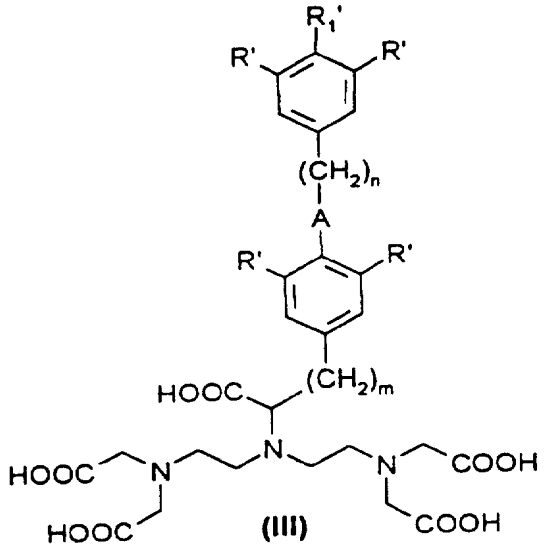
Among the compounds of formula (I) particularly preferred are the ones of formula (II),



(II)

in which R1 is H and R is as defined above in formula (I), but is different from H.

Among compounds of formula (II), preferred are the compounds of formula (III):



(III)

wherein:

R' = independently H, halogen;

R'_1 = H, OH, $N(R")_2$, COOR", $-CON(R")_2$, $-SO_3H$, $-SO_2NHR"$, C_1-C_6 alkyl, C_1-C_6 alkoxy;

A = direct bond (i.e. non intervening atom), -O-, C=O

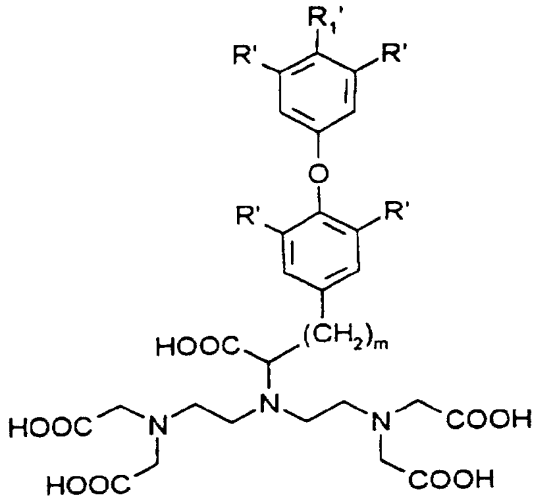
m = integer 1-6;

n = integer 0-2;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

with the proviso that, when R'_1 = H, at least one of the substituents R' is different from hydrogen.

Among compounds of formula (III), particularly preferred are the compounds of formula (IV)



(IV)

where:

R' = independently H, halogen;

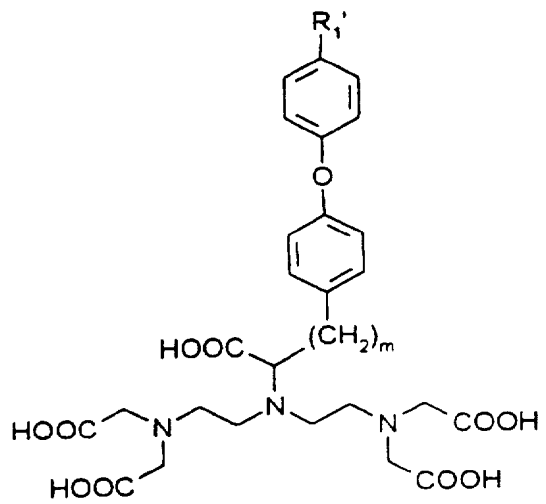
R'_1 = H, OH, $N(R")_2$, COOR", $-CON(R")_2$, $-SO_3H$, $-SO_2NHR"$, C_1-C_6 alkyl, C_1-C_6 alkoxy;

m = integer 1-6;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

with the proviso that at least one of the substituents R' is different from hydrogen,

as well as compounds of formula (V)



(V)

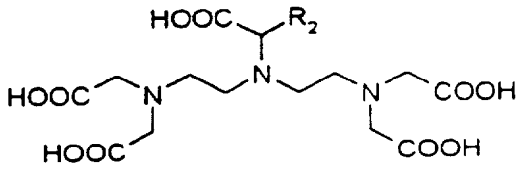
where:

R'_1 = OH, $N(R")_2$, COOR", $-CON(R")_2$, $-SO_3H$, $-SO_2NHR"$, C_1-C_6 alkyl, C_1-C_6 alkoxy;

m = integer 1-6;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups.

Among compounds of formula (II), preferred are also those of formula (VI)



(VI)

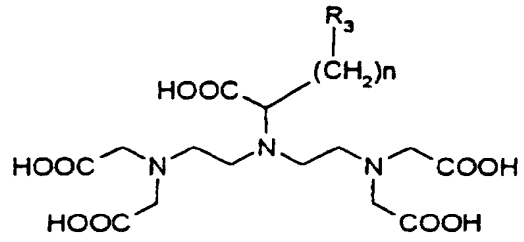
where:

R_2 = C_1-C_8 alkyl, optionally interrupted by one or more -CONH-, -NHCO-, -CO- groups and/or N, S atoms,

optionally substituted with -OH, -COOH, $-NH_2$, $-N(R")_2$ groups, said alkyl being interrupted or substituted with a polycyclic unit comprising from 2 to 3 saturated or unsaturated or aromatic fused rings, said polycyclic unit being interrupted by one or more N, O, S and optionally substituted with -OH, -COOH, $-NH_2$, $-N(R")_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{20} arylalkoxy groups;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

and particularly preferred are the compounds of general formula (VII)



(VII)

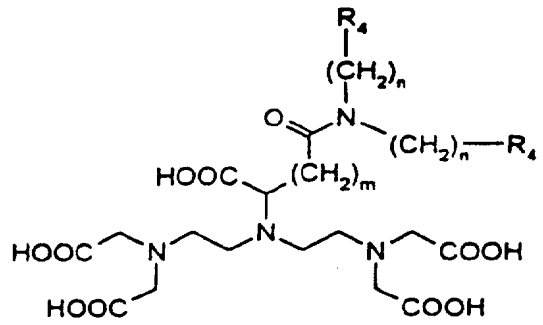
in which:

R_3 = a polycyclic unit comprising from 2 to 3 saturated or unsaturated or aromatic fused rings, said polycyclic unit being interrupted by one or more N, O, S and optionally substituted with -OH, -COOH, $-NH_2$, $-N(R")_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{20} arylalkoxy groups;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

n = integer 1-6.

Two further groups of preferred compounds, comprised within formula (II), are the compounds of formula (VIII)



(VIII)

in which:

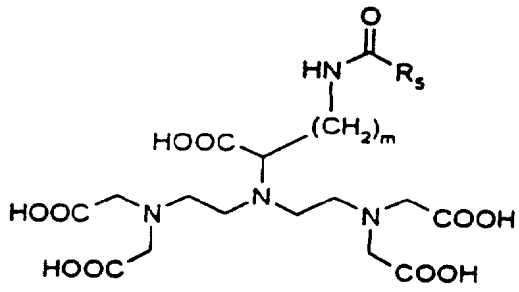
m = integer from 1 to 4;

n = independently integer from 0 to 2;

R_4 = independently saturated, unsaturated or aromatic ring, optionally interrupted by one or more N, O, S atoms and optionally substituted with one or more -OH, -COOH, $-NH_2$, $-N(R")_2$, $-CON(R")_2$, $-SO_3H$;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

and the compounds of formula (IX)



(IX)

in which:

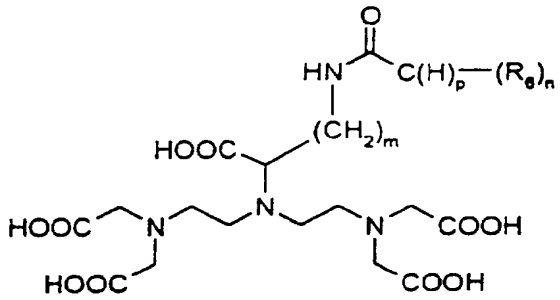
R_5 = C_1-C_3 alkyl, interrupted or substituted with 2 to

3 saturated, unsaturated or aromatic, isolated or fused rings, that are optionally interrupted by one or more N, O, S and optionally substituted with one or more -OH, -COOH, $-NH_2$, $-N(R")_2$, $-CON(R")_2$, $-SO_3H$;

R" = independently H or C_1-C_5 linear or branched alkyl, optionally substituted with 1 to 5 -OH groups;

m = 1-6.

Among compounds of general formula (IX), particularly preferred are the compounds of formula (X)



(X)

in which:

R_6 = saturated, unsaturated or aromatic 5- or 6-membered ring, optionally interrupted by one or more N, O, S;

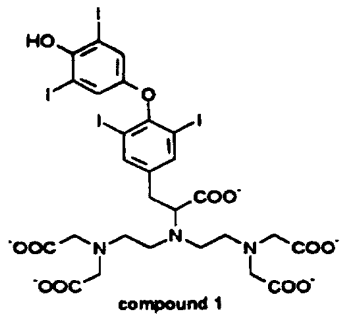
m = 1-6;

n = 2 or 3;

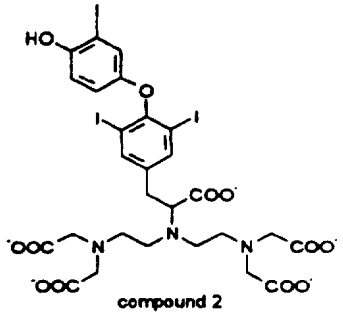
p = 0 or 1;

with the proviso that p+n=3.

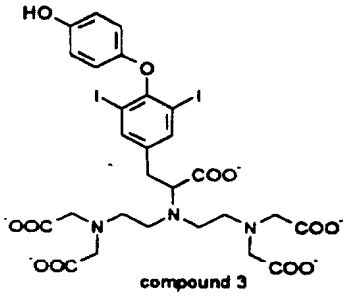
Among the compounds of formulae (III) and (IV), most preferred are the compounds from 1 to 3 of formula:



compound 1

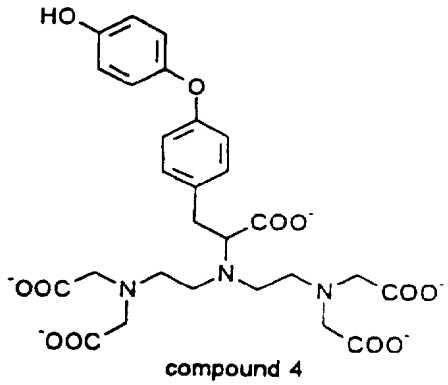


compound 2



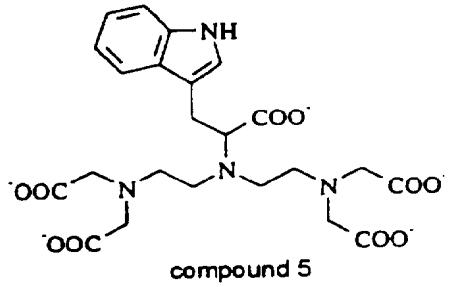
compound 3

Among the compounds of formula (V), most preferred is compound 4 of formula:



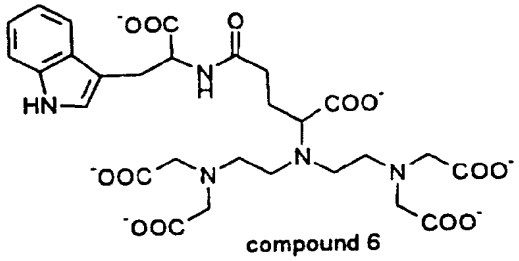
compound 4

Among the compounds of formula (VI), most preferred is compound 5 of formula:



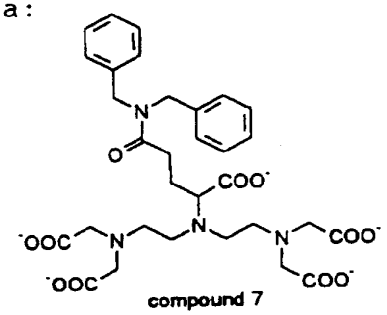
compound 5

Among the compounds of formula (VII), most preferred is compound 6 of formula:

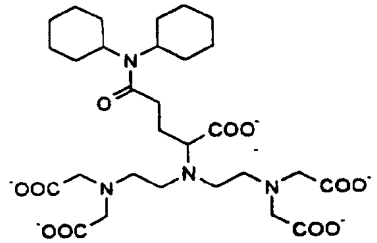


compound 6

Among the compounds of formula (VIII), most preferred are compounds 7 and 8, respectively of formula:

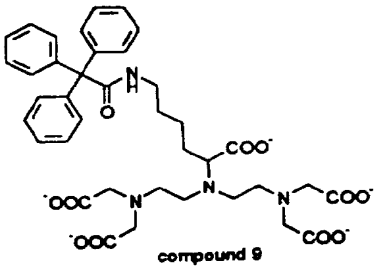


compound 7

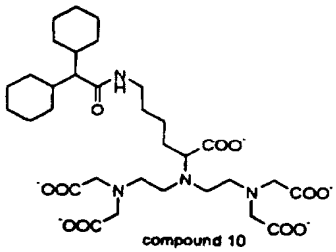


compound 8

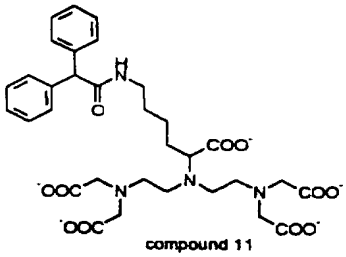
and among the compounds of formulae (IX) and (X), most preferred are compounds from 9 to 11 of formulae



compound 9



compound 10



compound 11

respectively.

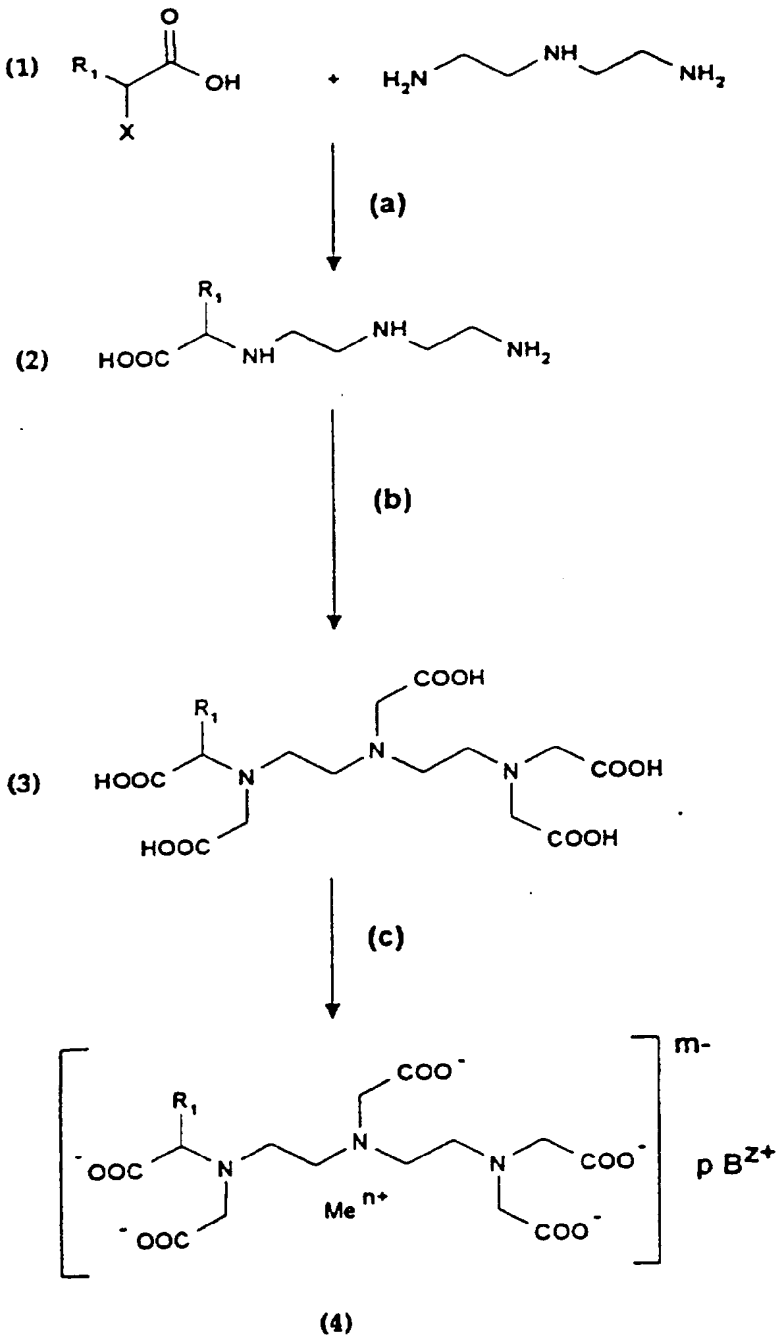
The preparation of the compounds of the present application comprises the regiospecific introduction of

the hindering substituent in α to a carboxylic group of the acetic acid bound to the central nitrogen atom of DTPA.

One of the preferred synthetical ways used refers to that introduced by Rapoport (J. Org. Chem. 1993, 58, 1151-1158), starting from natural or synthetical α-amino acid derivatives. An alternative way comprises the use of synthons such as glutamic acid or lysine, which allows the introduction of hindering groups quite distant from the carbon atom in α to a carboxylic group of the central acetic acid residue, exploiting the terminal acid or amino functions, respectively, of a.m. amino acids.

Starting from suitable precursor synthons it is also possible make use of the synthesis disclosed in US 5,514,510.

As far as the introduction of the hindering substituent at the α- position to the carboxylic group of one of the acetic groups bound to the side nitrogen atoms of DTPA is concerned, the synthesis scheme below can be followed:



wherein R_1 is as defined above for compounds of general formula (I).

The synthesis comprises the following steps:

(a) precursor (1), wherein X = Cl, Br or other leaving groups, is reacted with a diethylenetriamine excess in water, at a temperature of about 50°C, to obtain almost selectively compound (2), which is reacted in step

(b) with sodium bromoacetate in water at pH 10, to give the pentaacid (3), which is reacted, in the subsequent step

(c) with a suitable oxide or salt of a metal having atomic number comprised from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83 (such as Gd_2O_3, $GdCl_3$) e with the appropriate amount of a physiologically acceptable organic base (such as meglumine) or of an inorganic base the cations of which are sodium, potassium, magnesium, calcium, or mixtures thereof, to give the final compound (4),

wherein:

Me^{n+} = ion of the metal element having atomic number comprised from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83 (such as Gd^{3+});

n = number of the positive charges of said ion;

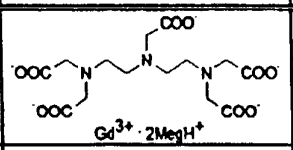
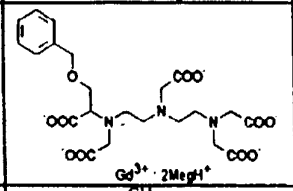
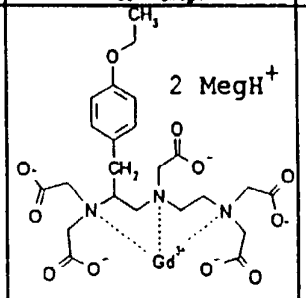
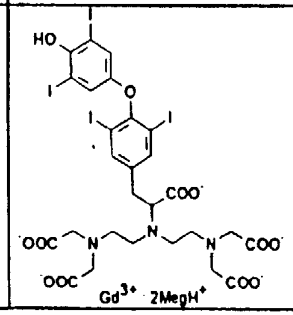
m = number of the overall negative charges of the metal chelate;

B^{z+} = Na^+, K^+, Mg^{++}, Ca^{++} or mixtures thereof, or it is the salt of a physiologically acceptable organic base;

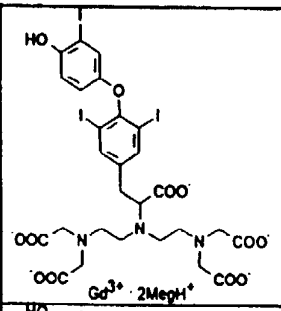
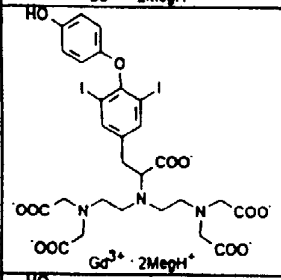
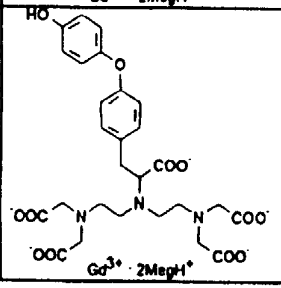
z = number of the positive charges of B;

p = an integer so that: p x z = m.

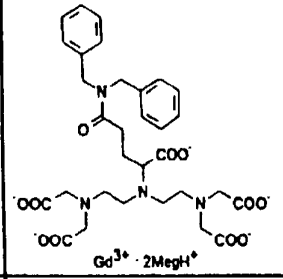
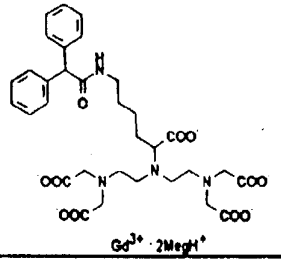
TABLE 1

Compound	Structure	Relaxivity ($mM^{-1}s^{-1}$)			
		Saline (*)		Serum (**)	
		r_1	r_2	r_1	r_2
Gd-DTPA/Dimeg		3.77	4.73	4.96	5.43
Gd-BOPTA(§)/Dimeg		4.39	5.56	10.8	12.2
Gd-EOB-DTPA(♦) /Dimeg		5.43	6.15	11.00	12.60
Compound 1 Gd complex, dimeg. salt		17.0	19.0	34.3	39.6

- continued -

Compound 2 Gd complex, dimeg. salt		12.7	15.0	36.2	42.2
Compound 3 Gd complex, dimeg. salt		6.3	7.0	37.0	42.2
Compound 4 Gd complex, dimeg. salt		5.47	6.27	25.6	29.4

- continued -

Compound	Structure	Relaxivity ($mM^{-1}s^{-1}$)			
		Saline (*)		Serum (**)	
		r_1	r_2	r_1	r_2
Compound 7 Gd complex, dimeg. salt		5.51	6.18	20.2	23.7
Compound 11 Gd complex, dimeg. salt		5.70	6.45	20.1	23.3

(*) NaCl 0.15 M in water - pH 7.3 - 20 MHz - 39°C

(**) Between 0 and 1 mM (Seronorm^{TM}Human) - 20 MHz - 39°C

(§) Bracco EP-B 230893

(♦) Schering EP 405704

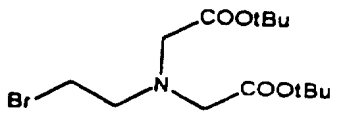
Table 1 above discloses the high relaxivity shown in serum by the compounds of the present application; r_1 and r_2 relaxivity values of some of the preferred compounds are reported, in comparison with the corresponding r_1 and r_2 values measured for some of the mayor prior-art compounds: Gd-DTPA Dimeglumine salt (MAGNEVIST(R)); Gd-BOPTA Dimeglumine salt and Gd-EOB-DTPA Dimeglumine salt.

The data of Table 1 clearly show that the compounds of the present invention have surprisingly high relaxivity values r_1 and r_2, measured in Seronorm™ Human.

This is particularly interesting from the application point of view, both as far as the improvement in the obtainable images, the development of formulations specific to particular districts and the determination of optimum low dosages of the contrast medium are concerned.

EXAMPLE 1

N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester



Ethanolamine (15.15 g; 0.25 mol) was dropped in 10 minutes into a suspension of t-butyl bromoacetate (112.3 g; 0.58 mol) and $KHCO_3$ (62.57 g; 0.62 mol) in DMF (400 mL), maintained at 0°C under inert atmosphere. After 22 h at 20°C the suspension was diluted with a saturated solution of $NaHCO_3$ (400 mL) and Et_2O (400 mL). After separation, the aqueous phase was extracted with Et_2O

(800 mL); the organic phases were collected, dried (Na_2SO_4) and concentrated. The obtained oil (100 g) was dissolved in CH_2Cl_2 (700 mL), then triphenylphosphine was added (79,76 g; 0,30 mol). To the solution, cooled to 0°C, solid NBS was slowly added (53,4 g; 0,30 mol). After 2.5 h the solution was concentrated to dryness and diluted with Et_2O (500 mL); the salts were filtered off, the solution was diluted with Et_2O (500 mL), then left at 4°C for 16 h. The salts were filtered off and the solution was concentrated; the oily residue (100 g) was purified by flash chromatography (silica gel; 95:5 n-hexane/EtOAc). The fractions having comparable purity were collected and evaporated to dryness, obtaining the desired compound (57 g; 0,16 mol). Yield 65%.

Gaschromatographic titre: 99 % (area %) - Chromatographic method:

Stationary phase: DB 5 (OV-73);

Film thickness: 0,25 µm;

Column: 30 m x 0,25 mm;

He flow rates at 130°C:

column flow rate 0,9 $mL \cdot min^{-1}$;

split flow rate 100 $mL \cdot min^{-1}$;

column flow rate + make-up 30 $mL \cdot min^{-1}$;

septum purge flow rate 3 $mL \cdot min^{-1}$;

Detector feeding (FID):

H_2 pressure 1,2 bar;

Air pressure 2,8 bar;

Temperature timetable:

1^{st} isotherm 50°C for 0 min;

gradient 10°C·min^{-1};

2^{nd} isotherm 150°C for 10 min;

Injector temperature: 150°C;

Detector temperature: 200°C;

Injection: 1 µL;

Sample concentration: 30 $mg \cdot mL^{-1}$

TLC: Rf 0,4

Stationary phase: silica gel

Mobile phase: 9:1 n-hexane: EtOAc (v/v)

Detection: 0.5% $KMnO_4$ (w/w) in 1 N NaOH

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

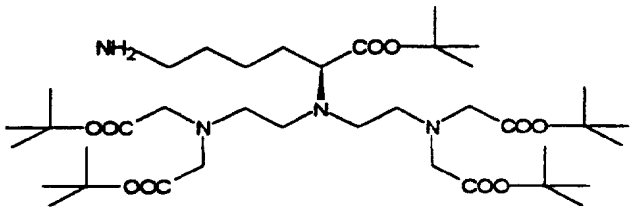
K.F.: 0,1% (w/w)

Elemental analysis (%):

	C	H	N	Br
Calcd.	47.73	7.44	3.98	22.68
Found	47.86	7.50	4.03	22.49

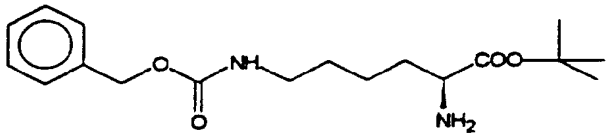
EXAMPLE 2

N^2,N^2-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxoethyl]-amino]ethyl]L-lysine 1,1-dimethylethyl ester



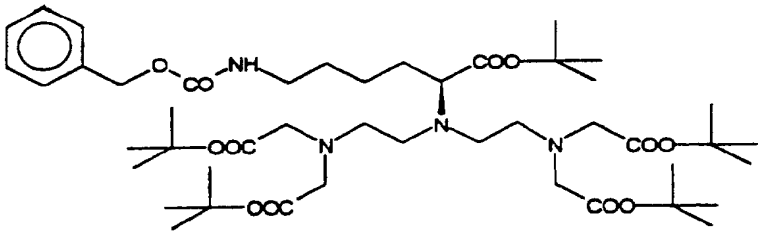
A) N^6-[(Phenylmethoxy)carbonyl]-L-lysine-1,1-dimethylethyl ester

C.A.S. [21957-42-6]



The compound was prepared according to: Bentley, P.H.; Stachulski, A. V.. J. Chem. Soc. Perkin Trans. I 1983, 1187-1192.

B) N^6-[(Phenylmethoxy)carbonyl]-N^2,N^2-bis[2-[bis[2-(1,1-dimethylethoxy)2-oxoethyl]amino]ethyl]-L-lysine 1,1-dimethylethyl ester



N^6-[(Phenylmethoxy)carbonyl]-L-lysine 1,1-dimethylethyl ester (80.6 g; 0.24 mol) and N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (209 g; 0.59 mol) (prepared according to Example 1) were dissolved in MeCN (900 mL). After addition of 2 M pH 8 phosphate buffer (1000 mL) the mixture was vigorously stirred for 2 h. The two phases were separated and the aqueous phase replaced with fresh 2 M pH 8 phosphate buffer (80 mL). After stirring for 48 h the mixture was separated and the organic phase concentrated to dryness, to give a residue which was dissolved in CH_2Cl_2 (1000 mL). The solution was washed with H_2O (2 x 50 mL), then dried and concentrated to yield an oil which was purified by silica gel chromatography:

Silica gel column

Stationary phase: Silica gel 230-400 mesh Merck KGaA art. 9385

Mobile phase 4 : 1 n-hexane/EtOAc

The desired product (190 g; 0.216 mol) was obtained. Yield 90 %.

The product was utilised for the following step without further purification.

Acidic titer (0.1 N $HClO_4$ in CH_3COOH) : 96.8 %

TLC : Rf 0.22

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 2/1 n-hexane/EtOAc

Detection: 1% $KMnO_4$ in 1 N NaOH

HPLC : 95.1 % (area %) - Chromatographic method:

Stationary phase: Lichrosorb RP-Select B 5 µm; 250 x 4 mm column packed by Merck KGaA;

Temperature: 45°C;

Mobile phase: gradient elution;

A = 0.01 M KH_2PO_4 and 0.017 M H_3PO_4 in water

B = CH_3CN

Gradient timetable:

min	% A	% B
0	90	10
35	40	60
40	40	60
43	30	70
50	30	70

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation : Merck KGaA - Hitachi high pressure

gradient pump system (two Lachrom L 7100 pumps), Merck KGaA - Hitachi Lachrom L 7200 autosampler, Merck KGaA - Hitachi Lachrom L 7300 column thermostat, Merck KGaA - Hitachi Lachrom L 7400 UV detector.

K.F. : < 0.10%

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$ (c 4.98; $CHCl_3$)

$\lambda_{(nm)}$	589	578	546	436	405	365
$[\alpha]_{\lambda}^{20}$	-26.40°	-28.03°	-32.13°	-57.81°	-71.44°	-98.87°

Elemental analysis (%):

	C	H	N
Calcd.	62.85	8.94	6.37
Found	63.04	9.20	6.27

C) N^2,N^2-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]amino]ethyl]-L-lysine 1,1-dimethylethyl ester

To a solution of the product from the previous preparation (180 g; 0.2 mol) in MeOH (1 L), 5% Pd on carbon (commercial product) (9 g) was added. The suspension was stirred for 4 h under a hydrogen atmosphere at 20°C (consumed H_2 3900 mL; 0.174 mol). The mixture was filtered over Millipore(R) HA 0.45 µm, washed with MeOH and the solution was evaporated. The residue was dissolved in 0.5 N HCl and the solution was maintained under vacuum for 10 min, then 1 N NaOH was added and the product was extracted with Et_2O. The solution was evaporated and the residue was purified by silica gel chromatography:

Silica gel column

Stationary phase: Silica gel 230-400 mesh Merck KGaA art 9385 (600 g)

Mobile phase: MeOH

The desired compound (90 g; 0.121 mol) was obtained.

Yield 60 %

Acidic titer (0.1 N HCl) :

first inflection point 93.7 %;

Second inflection point 95.3 %;

Equivalent points pH 7.3 and 7.8

TLC : Rf 0.08

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: MeOH

Detection: 1% $KMnO_4$ in 1 N NaOH

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$(c 5.07; $CHCl_3$)

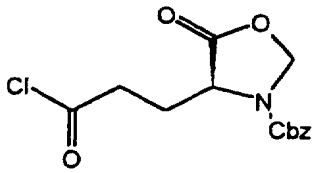
$\lambda_{(nm)}$	589	578	546	436	405	365
$[\alpha]_{\lambda}^{20}$	-27.19°	-28.77°	-33.24°	-59.98°	-74.88°	-104.67°

Elemental analysis (%):

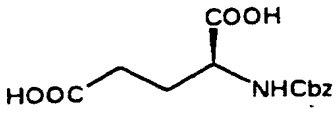
	C	H	N
Calcd.	61.26	9.74	7.52
Found	61.43	10.25	7.48

EXAMPLE 3

(S)-5-Oxo-3-[(phenylmethoxy)carbonyl]-4-oxazolidine-propanoyl chloride



A) N-[(Phenylmethoxy)carbonyl]-L-glutamic acid



A suspension of L-glutamic acid (23.5 g; 160 mmol) in H_2O (100 mL) was stirred, maintaining the pH at 8.5 with 10 M NaOH until complete dissolution. Benzyl chloroformate (35 g; 205 mmol) was added over 15 min to the clear solution. The mixture was stirred, maintaining the pH at 9 by adding 10 M NaOH until the reaction was complete. The cloudy mixture was washed with Et_2O (3x150 mL) and then the pH of the resulting solution was adjusted to 2.1 with 1 M HCl. The cloudy aqueous mixture was extracted with Et_2O (2x200 mL), the organic layers were collected and evaporated to yield the desired product (39.13 g; 139 mmol). Yield 87%.

HPLC : 97% (area %) - Chromatographic method:

Stationary phase: Lichrosorb RP-Select B 5 µm; 250 x 4 mm column packed by Merck KGaA;

Temperature: 45°C;

Mobile phase: gradient elution;

A = 0.017 M H_3PO_4 in water

B = CH_3CN

Gradient timetable:

min	% A	% B
0	95	5
5	95	5
30	20	80
45	20	80

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation : Merck KGaA - Hitachi L 6200 low pressure gradient pump, Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T6300 column thermostat, Merck KGaA - Hitachi L 4000 UV detector.

TLC : Rf 0.3

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 6:3:1 $CHCl_3$:MeOH:25% aq. NH_4OH

Detection: 1% $KMnO_4$ in 1 M NaOH

B) (S)-5-Oxo-3-[(phenylmethoxy)carbonyl]-4-oxazolidinepropanoyl chloride

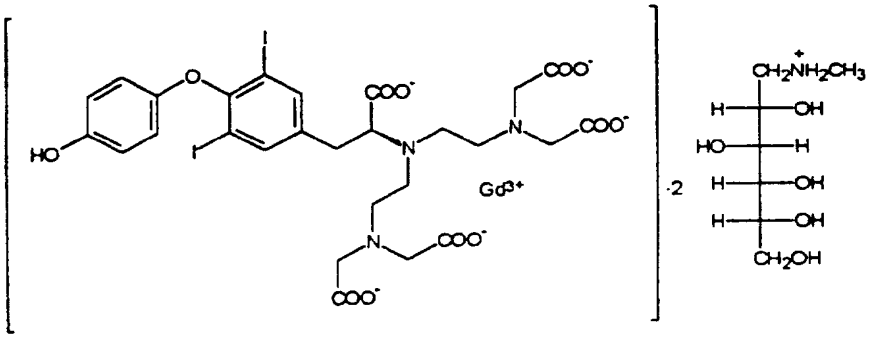
A suspension of the product from the previous preparation (30 g; 107 mmol), paraformaldehyde (6 g) and PTSA (0.3 g) in toluene (400 mL) was refluxed in a Dean Stark trap. When the water evolution was over the hot cloudy mixture was filtered and the resulting clear solution was evaporated under reduced pressure (2 kPa). The oily residue was dissolved in $SOCl_2$ (150 mL). The mixture was stirred at r.t. for 3 h, then carefully evaporated under reduced pressure (2 kPa) to yield an oil that became solid on standing overnight at 4°C. The crude was slurried with hexane (200 mL) and then with Et_2O (150 mL) to yield the title compound (21.7 g; 69 mmol). Overall yield 65%.

HPLC: 95.7 % (area %) - Chromatographic method: the same of previous step A)

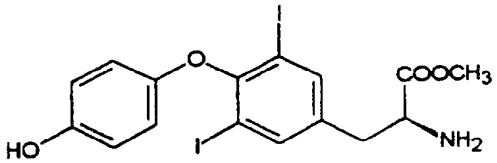
Argentometric titer (0.1 M $AgNO_3$): 98.2%

EXAMPLE 4

[[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosinato(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)



A) O-(4-Hydroxyphenyl)-3,5-diiodo-L-tyrosine methyl ester



A 6 M solution of HCl in MeOH (8 mL; 4.8 mmol) was added to a suspension of O-(4-hydroxyphenyl)3,5-diiodo-L-tyrosine (2.12 g; 5 mmol) (prepared according to: Chalmers J.R., Dickson G.T., Elks J. and Hems D.A., "The Synthesis of Thyroxine and Related Substances", Part V., J. Chem. Soc. (1949), 3424-3433) in MeOH (12 mL). The resulting clear solution was stirred for 4 days at 20°C. Then a $NaHCO_3$ satured aqueous solution was added to the mixture until pH 7 was reached, obtaining a precipitate which was filtered. By concentration of the solution a second crop of precipitate was obtained. The two samples were combined and dried (50°C; 1.3 kPa) to give the

desired compound (2 g; 3.7 mmol). Yield 87%.

mp : 173°C.

Acidic titer (0.1 M $HClO_4$) : 96.1 %

HPLC: 98.4 % (area %) - Chromatographic method:

Stationary phase: Lichrosorb RP-Select B 5 (?)m;

250 x 4 mm column packed by Merck KGaA;

Temperature: 45°C;

Mobile phase: gradient elution;

A = 0.017 M H_3PO_4 in water

B = CH_3CN

Gradient timetable:

min	% A	% B
0	95	5
5	95	5
30	20	80
45	20	80

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation : Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector.

TLC : Rf 0.64

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase 9:1 CH_2Cl_2:MeOH

Detection 1 % $KMnO_4$ in 1 M NaOH

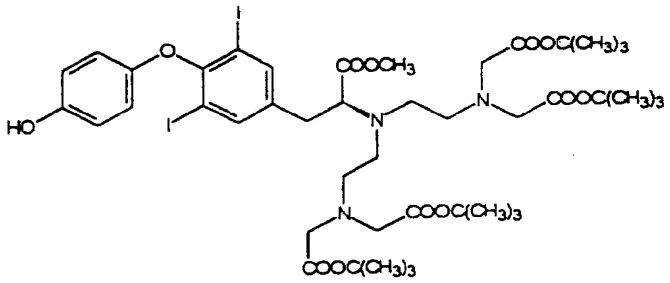
^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

KF : 0.44 %

Elemental analysis (%)

	C	H	I	N	Cl	
Calcd.	36.65	2.80	47.08	2.60	- -	
Found	35.32	2.72	45.60	2.57	< 0.1	anhydrous

B) N,N-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine methyl ester



The ester from the previous preparation (34 g; 95 mmol) and N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester, prepared according to Example 1, (67 g; 190 mmol) were dissolved in CH_3CN (1 L) and 2M pH 7 phosphate buffer (1 L) was then added. The mixture was vigorously stirred for 2 days then, after separation, further N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (10 g; 28 mmol) and fresh 2M pH 7 phosphate buffer (1 L) were added to the organic phase and the mixture was stirred for 16 h. After a further addition of N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (13 g; 37 mmol) the mixture was stirred for 8 h. After separation the organic phase was evaporated to dryness

(35°C; 1.3 kPa). The residue was suspended in CH_2Cl_2 (750 mL) and washed with brine (260 mL) and with H_2O (30 mL). The clear organic phase was dried (Na_2SO_4) and evaporated to yield an oil (125 g) which was purified by flash chromatography (Stationary phase: silica gel 230-400 mesh Merck KGaA art 9385 (1 kg; 100 x 250 mm). Mobile phase: 7:3 n-hexane: EtOAc (10 L)). The desired compound was obtained (77 g; 71 mmol). Yield 75 %

Acidic titer (0.1 M $HClO_4$) : 96.4 %

TLC : Rf 0.28

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 7:3 n-hexane:EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 98 % (area %) Chromatographic method: the same of previous step A)

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$(c 0.98; $CHCl_3$):

λ (nm)	589	578	546	436	405	365
$[\alpha]_\lambda^{20}$	-35.69°	-38.64°	-44.13°	-79.21°	-97.62°	-134.47°

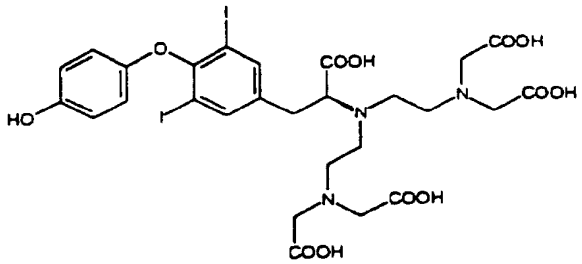
KF : 0.29 %

Elemental analysis (%):

	C	H	I	N	
Calcd.	48.85	6.06	23.46	3.88	
Found	49.13	6.18	22.99	3.85	anhydrous

C) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine

35



A suspension of the pentaester from the previous preparation (74.5 g; 69 mmol) in 0.25 M H_2SO_4 (1.65 L; 412 mmol) was stirred at 90°C for 4 h. The resulting hot solution was filtered and then cooled to room temperature to yield a white suspension. The pH was adjusted to 13.5 by adding 10 M NaOH (150 mL, 1.5 mol) and the mixture was stirred at 20°C for 5 h obtaining a clear solution. The pH was adjusted to 2.25 by adding 9 M H_2SO_4 and the resulting suspension was filtered to yield the free ligand (56 g; 67 mmol). Yield 97 %.

mp : 178°C (dec.)

Acidic titer (0.1 M $HClO_4$): 102 %

Complexometric titer (0.001 M $GdCl_3$): 99.7 %

HPLC : 99 % (area %) - Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm; 250 x 4 mm column packed by Merck KGaA;

Temperature: 40°C;

Mobile phase: isocratic elution with premixed mobile phase is obtained by addition of n-octylamine (1 g) and 0.1 M EDTA disodium salt (10 mL) to a mixture of CH_3CN (300 mL) and H_2O (790 mL) buffering to pH 6 with H_3PO_4;

Flow rate: 1 mL min^{-1};

Detection (UV): 245 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation: Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector, Merck KGaA.

TLC : Rf 0.44

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 4:4:2 $CHCl_3$:MeOH:25% aqueous NH_4OH

Detection: 1% $KMnO_4$ in 1 M NaOH

K.F. : 0.87 %

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$(c 2.48; 1 N NaOH):

λ (nm)	589	578	546	436
$[\alpha]_{\lambda}^{20}$	- 4.16°	- 4.24°	- 4.32°	- 4.52°

Elemental analysis (%):

	C	H	I	N	S	
Calcd.	38.45	3.71	30.09	4.98	- -	
Found	38.21	3.63	29.37	4.88	< 0.1	anhydrous

D) [[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosinate(5-)]gadolinate-(2-)] dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

A 1 M solution of 1-deoxy-1-(methylamino)-D-glucitol (67.7 mL; 67.7 mmol) was added to a stirred suspension of the free ligand from the previous preparation (22 g; 25 mmol) in H_2O (600 mL), obtaining

complete dissolution. A solution of $GdCl_3 \cdot 6\ H_2O$ (9.3 g; 25 mmol) in H_2O (20 mL) was then added dropwise maintaining the pH at 5.5 with 1 M 1-deoxy-1-(methylamino)-D-glucitol. The resulting solution was filtered over Millipore(R) (HAWP 0.45 µm) and loaded onto a column of Amberlite(R) XAD-1600 polystyrene resin (1 L). The resin was eluted with H_2O (3 L) and then with 95:5 H_2O:CH_3CN. The eluate was filtered over Millipore(R) (HAWP 0.45 µm), concentrated to 40 mL and, after adjusting the pH to 7.2 with 0.1 M HCl, was evaporated to dryness (1.3 kPa; 40°C; P_2O_5) to yield the title compound (30.5 g; 21.9 mmol). Yield 87%

mp : 193°C (dec.)

Free ligand (0.001 M $GdCl_3$) : < 0.1 %

HPLC : 99 % (area %) Chromatographic method: the same of previous step C)

K.F. : 2.08 %

MS spectrum was consistent with the structure.

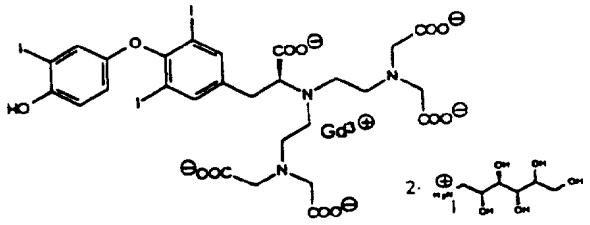
Elemental analysis (%):

	C	H	Gd	I	N	
Calcd.	35.48	4.50	11.33	18.29	5.05	
Found	35.69	4.47	11.55	18.49	5.02	anhydrous

EXAMPLE 5

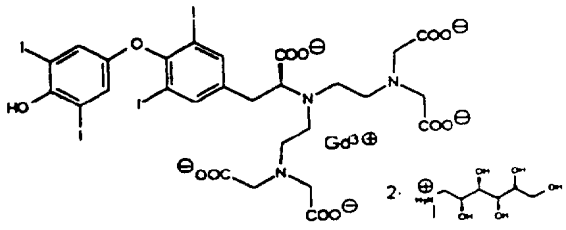
Preparation of the two compounds:

[[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

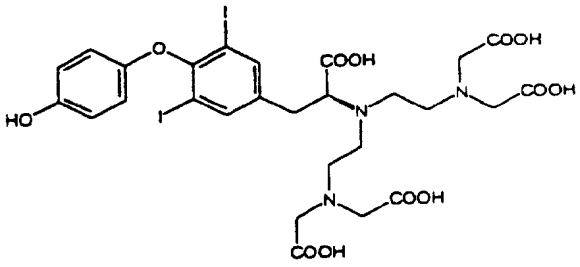


and

[[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)



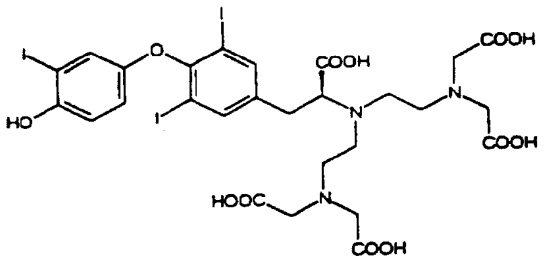
A) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine (B 21920)



The compound was prepared according to Example 4.

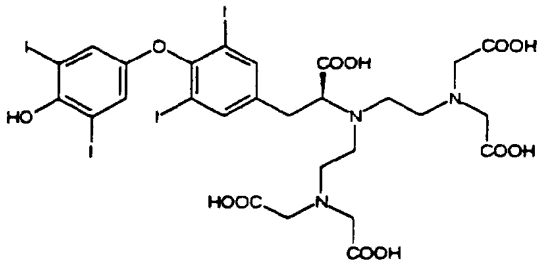
B)

1) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosine



and

2) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine



1 M NaOH (58.6 mL) was added at 20°C to a suspension of N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine (12.67 g; 15 mmol) in H_2O (150 mL) until pH 10 was reached. A solution of I_2 (12.69 g; 50 mmol) and KI (21.58 g; 130 mmol) in H_2O (100 mL) (47.7 mL; 23.7 mmol) was added dropwise to the resulting solution over 4.5 h, maintaining pH 10 by the addition of 1 M NaOH through a pH-stat apparatus. The mixture was filtered over Millipore(R) HA 0.45 m and acidified to pH 0 with 37% HCl (42 mL; 0.5 mol) to yield a precipitate that was filtered and dried (50° C; 1.3 kPa; P_2O_5) (13.3 g). The solid was suspended in H_2O, then dissolved by adding 2 M NaOH up to pH 9 and acidified with 2 M HCl to pH 5, then it was purified by preparative HPLC:

Preparative Chromatographic method:

Stationary phase: Lichroprep RP-8 25-40 µm;
250 x 50 mm column;
Temperature: room temperature;
Mobile phase: stepped gradient elution;

A = 0.01 M KH_2PO_4

B = 0.01 M KH_2PO_4/CH_3CN 8/2

C = H_2O/CH_3CN 1/1

Step timetable:	start (min)	end (min)	% A	% B	%C	flow rate (mL min^{-1})
	0	15	100	0	0	60
	15	92	0	100	0	60
	92	110	0	0	100	60
	110	130	100	0	0	60

Detection (UV): 210 nm;

UV detector attenuation: 256;

Injection: 100 mL;

Sample concentration: 10 mg mL^{-1};

Instrumentation : Merck KGaA Prepbar 100

The two crude ligands were separately suspended in water (250 mL) and dissolved by the addition of 10 M NaOH up to pH 6. Acidification of the two solutions to pH 2.5 with 37% HCl led to formation of two precipitates which were filtered and dried (50° C; 1.3 kPa; P_2O_5) to yield the product (B1) (3,1 g; 3.2 mmol; yield 21%) and (B2) (2.7 g; 2.5 mmol; yield 17%).

COMPOUND B1:

mp : 188°C (dec.)

Acidic titer (0.1 N $HClO_4$) : 95.5%

Complexometric titer (0.001 M $GdCl_3$) : 96.6 %

HPLC : 99 % (area %) Chromatographic method: the same of Ex. 4, step A)

K.F. : 3.84 %

^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

Elemental analysis (%):

	C	H	I	N	
Calcd.	33.36	3.12	39.28	4.34	
Found	33.34	2.91	39.14	4.33	anhydrous

COMPOUND B2:

mp : 194°C (dec.)

Complexometric titer (0.001 M $GdCl_3$) : 96.4 %

HPLC : 98.6 (area %) Chromatographic method: the same of Ex. 4, step A)

K.F. : 3.07%

^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

Elemental analysis (%):

	C	H	I	N	
Calcd.	29.31	2.67	46.35	3.84	
Found	29.31	2.57	45.33	3.78	anhydrous

C1) [[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosinate(5-)]-gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol (5.4 mL; 5.4 mmol) was dropped into a suspension of compound B1 (B 22090) (1.94 g; 2 mmol) in H_2O (100 mL), stirring until complete dissolution. A 0.33 M solution of $GdCl_3$ (6.2 mL; 2.05 mmol) was slowly added, maintaining the pH of the mixture at 6.5 by addition of a 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol through a pH-stat apparatus. After stirring for 1 h at room temperature the cloudy solution was filtered over Millipore(R) HA 0.45 m. The solution was loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (200 mL) and the column eluted with H_2O (1 L) followed by 3/1 H_2O/CH_3CN mixture (1 L). The fractions containing the complex were combined and concentrated to 150 mL. The resulting solution was filtered over Millipore(R) HA 0.45 m and evaporated to dryness to give the title compound (2.2 g; 1.45 mmol). Yield 76 %.

mp : 163°C (dec.)

Free ligand (0.001 M $GdCl_3$) : <0.1 %

HPLC : 99.2 (area %) - Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;

250 x 4 mm column packed by Merck KGaA;

Temperature: 40°C;

Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 350 mL of acetonitrile mixed with 650 mL of water. The solution is buffered to pH 6 with H_3PO_4

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm

Injection: 10 µL

Sample concentration: 1 mg mL^{-1}

Instrumentation: Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector.

K.F. : 4.18 %

Elemental analysis (%):

	C	H	Gd	I	N	
Calcd.	32.53	4.06	10.39	25.14	4.63	
Found	32.45	4.00	10.38	25.01	4.59	anhydrous

C2) [[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosinate-(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol (4.6 mL; 4.6 mmol) was dropped into a suspension of compound B2 (1.53 g; 1.4 mmol) in H_2O

(100 mL), stirring until complete dissolution. A 0.33 M solution of $GdCl_3$ (4.2 mL; 2.05 mmol) was slowly added, maintaining the pH of the mixture at 6.5 by addition of a 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol through a pH-stat apparatus. After stirring for 1 h at room temperature the solution was filtered over Millipore(R) HA 0.45 m and loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (200 mL); the column was eluted with H_2O (1 L) followed by 3/1 H_2O/CH_3CN mixture (1 L). The fractions containing the complex were combined and, after concentration to 150 mL, filtered over Millipore(R) HA 0.45 m. The solution was evaporated to dryness to give the title compound (1.85 g; 1.13 mmol). Yield 81 %.

mp : 153°C (dec.)

Free ligand (0.001 M $GdCl_3$) : <0.1 %

HPLC : 98.8 (area %) Chromatographic method: the same of previous step C1)

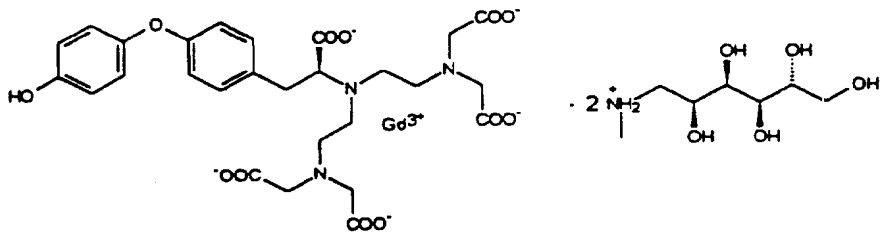
K.F. : 1.73 %

Elemental analysis (%):

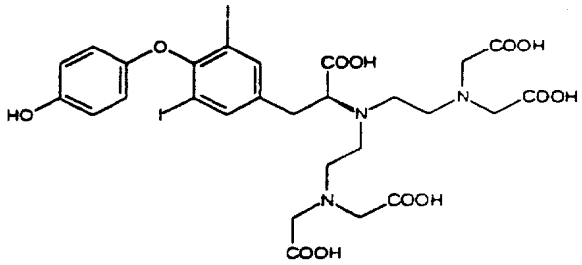
	C	H	Gd	I	N	
Calcd.	30.03	3.69	9.59	30.96	4.27	
Found	29.78	3.81	9.43	30.59	4.21	anhydrous

EXAMPLE 6

[[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-L-tyrosinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

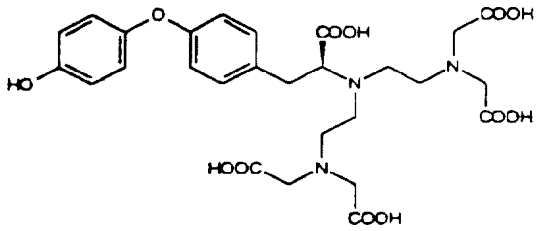


A) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine



The compound was prepared according to Example 4.

B) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-L-tyrosine



To a suspension of N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine (5,1 g; 6 mmol) 1 M NaOH (15 mL; 15 mmol) was added until pH 7 then Pd on carbon (3 g) was added. The suspension was stirred over 90 min under a hydrogen atmosphere (consumed H_2 300 mL; 12.2 mmol) at 26°C and atmospheric pressure, maintaining pH 7 by the addition of 1 M NaOH (11.33 mL; 11.33 mmol) through a pH-stat apparatus. The suspension was filtered over Millipore(R) HA 0.45 m and 6 M HCl (7 mL; 42 mmol) was added to the

solution down to pH 0.5, then the mixture was loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (1 L). The column was eluted with H_2O until I^- ions were not detectable in the eluate any more, then washed with 2% aqueous $NaHSO_3$ (100 mL) and H_2O (2 L); elution with 8/2 H_2O/CH_3CN afforded the product. After evaporation of the solvent the amorphous residue was suspended in CH_3CN and the solvent evaporated. Such procedure was repeated until the desired compound was recovered by filtration (3.07 g; 5.2 mmol). Yield 86 %.

mp : 134°C (dec.)

Acidic titer (0.1 N $HClO_4$) : 100.5%

Acidic titer (0.1 N NaOH) : 97.3%

Complexometric titer (0.1 N $ZnSO_4$) : 96 %

TLC : Rf 0.3

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 4/4/2 $CHCl_3/CH_3OH$/25 % aqueous NH_4OH

Detection: 1 % $KMnO_4$ in 1 M NaOH

HPLC : 99.5 (area %) Chromatographic method: the same of Ex.4, A)

K.F. : 1.38 %

^{13}C-NMR, ^1H-NMR, MS and IR spectra were consistent with the structure.

Elemental analysis (%):

	C	H	N	I	
Calcd.	54.82	5.62	7.10	- -	
Found	54.17	5.62	7.57	<0.1	anhydrous

$[\alpha]^{20}$(c 2.55; 0.1 N NaOH):

λ (nm)	589	578	543	436	405	365
$[\alpha]_{\lambda}^{20}$	-3.13°	-3.17°	-3.53°	-5.95°	-6.42°	-7.17°

C) [N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroyphenyl)-L-tyrosinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol (25 mL; 25 mmol) was dropped into a suspension of the product from the previous preparation (5.32 g; 9 mmol) in H_2O (200 mL), stirring until complete dissolution. A 0.4 M solution of $GdCl_3$ (22 mL; 8.8 mmol) was slowly added, maintaining the pH of the mixture at 6.5 by addition of a 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol. After stirring for 1 h at room temperature the solution was filtered over Millipore(R) HA 0.45 m. The solution was loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (300 mL) and the column eluted with water followed by 9/1 H_2O/CH_3CN mixture. The fractions containing the complex were combined and, after concentration to 150 mL, filtered over Millipore(R) HA 0.45 m. The solution was evaporated to dryness to give the title compound as a white solid (7.79 g; 6.8 mmol). Yield 76 %.

mp : 125°C (dec.)

Free ligand (0.001 M $GdCl_3$) : <0.1 %

HPLC : 99.9 (area %) - Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;

250 x 4 mm column packed by Merck KGaA;

Temperature: 40°C;

Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 230 mL of

acetonitrile mixed with 770 mL of water. The solution is buffered to pH 6 with H_3PO_4;

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation: Merck KGaA - Hitachi L 6200 low pressure gradient pump, Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T6300 column thermostat, Merck KGaA - Hitachi L 4000 UV detector.

K.F. : 2.98 %

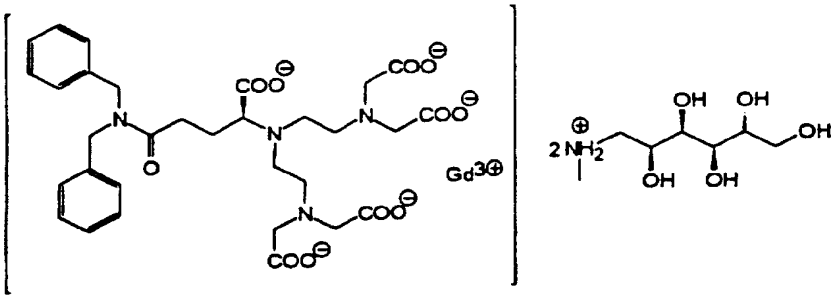
MS spectrum was consistent with the structure.

Elemental analysis (%):

	C	H	N	Gd	
Calcd.	43.34	5.68	6.16	13.84	
Found	43.50	5.72	6.15	13.89	anhydrous

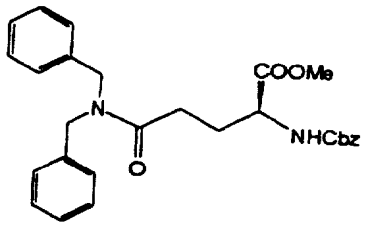
EXAMPLE 7

[[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[bis-(phenylmethyl)]-L-glutaminate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)



A) N^2-[(Phenylmethoxy)carbonyl]-N,N-[bis(phenylmethyl)]L-glutamine methyl ester

50



5

To a stirred solution of (S)-5-oxo-3-[(phenylmethoxy)carbonyl]-4-oxazolidinepropanoyl chloride, prepared according to Example 3, (33.3 g; 107 mmol) in $CHCl_3$ (250 mL) dibenzylamine was added dropwise (214 mmol; 42.2 g; 41 mL). The resulting mixture was filtered, the solution concentrated to 90 mL and again filtered. The clear solution was evaporated under reduced pressure (2 kPa) to provide (S)-5-oxo-4-[3-oxo-3-[bis(phenylmethyl)amino]propyl]-3-oxazolidinecarboxylic acid phenylmethyl ester (50.6 g; 107 mmol), that was not isolated. This intermediate was dissolved in MeOH (300 mL) and the resulting solution was added dropwise with a 1 M solution of MeONa (110 mmol; 110 mL) in MeOH. The resulting mixture was concentrated to 200 mL under reduced pressure (2 kPa) and then added to a stirred mixture of 1 M HCl (150 mL) and EtOAc (300 mL). The organic phase was washed with 1 M HCl (200 mL), dried (Na_2SO_4) and concentrated (2 kPa) to dryness. The crude (49 g) was purified by flash chromatography (Stationary phase: Silica gel 230-400 mesh Merck KGaA art 9385 (1 Kg). Mobile phase: 7:3 n-hexane:EtOAc (10 L)) to give the desired product (40 g; 84.3 mmol). Overall yield 79%.

TLC : Rf 0.25

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

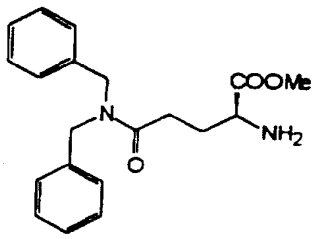
Mobile phase: 6:4 n-hexane:EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 99.7% (area %) Chromatographic method: the same of Ex. 3, Step A)

^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

B) N,N-[Bis(phenylmethyl)]-L-glutamine methyl ester



To a stirred suspension of the protected derivative from the previous preparation (38.2 g; 80 mmol) in acetic acid (80 mL) 33% HBr in acetic acid was slowly added (75 mL; 412 mmol) and the mixture was stirred until the gas evolution was over. The mixture was then carefully poured into H_2O (500 mL), adjusting the pH of the resulting mixture to 2 by the addition of 2 M NaOH. The solution was extracted with EtOAc (3x200 mL). The pH of the aqueous phase was adjusted to 7 by adding 2 M NaOH and the mixture was extracted with EtOAc (2x150 mL) to give a first solution containing the reaction product. The organic layers relative to the first extraction were extracted with 1 M HCl (3x200 mL). The aqueous phases were combined, the pH adjusted to 7.4 by adding 10 M NaOH and the resulting mixture extracted with EtOAc (3x200 mL) to yield a second solution of the reaction product. The two solutions were combined, dried (Na_2SO_4) and concentrated under reduced pressure (2 kPa) to give the desired amino ester derivative (23 g; 67.6

mmol). Yield 85%.

TLC : Rf 0.68

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

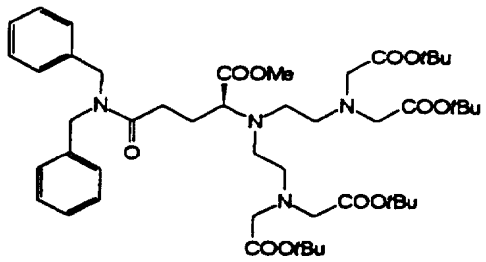
Mobile phase: 8:2 CH_2Cl_2/MeOH

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 98% (area %) Chromatographic method: the same of Ex. 3, Step A)

^{13}C-NMR and ^{1}H-NMR spectra were consistent with the structure.

C) N^2,N^2-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]amino]ethyl]-N,N-[bis(phenylmethyl)]-L-glutamine methyl ester



A 2 M pH 8 phosphate buffer (600 mL) was added to a solution of N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (45.6 g; 135 mmol) (prepared according to Example 1) and of the compound from the previous preparation (22 g; 64.5 mmol) in CH_3CN (500 mL). After 24 h of vigorous stirring the two phases were separated and the organic phase was evaporated under reduced pressure (2 kPa). The residue was dissolved in CH_2Cl_2 (300 mL). The resulting solution was washed with water (200 mL), dried (Na_2SO_4) and concentrated to dryness. The crude was purified by flash chromatography (Stationary phase: Silica gel 230-400

mesh Merck KGaA art 9385 (1000 g). Mobile phase: 7:3 n-hexane:EtOAc (10 L)) to give the desired compound (40.7 g, 46 mmol). Yield 71%.

HPLC : 98.6 % (area %) Chromatographic method: the same of Ex. 3, Step A)

TLC : Rf 0.7

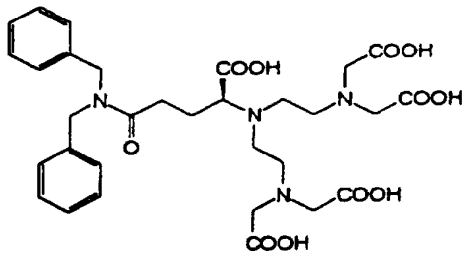
Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 6:4 n-hexane:EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

D) N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[bis(phenylmethyl)]-L-glutamine



0.5 M H_2SO_4 (500 mL; 250 mmol) was added to a suspension of the pentaester from the previous preparation (40.6 g; 46 mmol) in H_2O (400 mL); the resulting mixture was stirred at 60°C for 8 h, then at 90° C for 2 h. After cooling to r.t. the pH was adjusted to 13.5 by adding 10 M NaOH. After stirring for 2 h the pH of the mixture was adjusted to 6.0 by adding 98% H_2SO_4 and the clear solution was concentrated to a final volume of 200 mL. The pH was adjusted to 2 adding 98% H_2SO_4; then CH_3CN (30 mL) was added. The mixture was loaded onto a column of Amberlite(R) XAD 1600

polystyrene resin (1.5 L) conditioned with 7:1 H_2O/CH_3CN. The product was recovered by increasing the ratio of CH_3CN in the eluting mixture from 7:1 H_2O/CH_3CN to 1:1 H_2O/CH_3CN. The free ligand was obtained (18.5 g; 28.8 mmol). Yield 62%.

m.p. : 116°C

HPLC: 99% (area %) Chromatographic method: the same of Ex. 3, Step A)

^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

$[\alpha]^{20}$(c 4.0, 0.1 M NaOH)

λ (nm)	589	578	546	436	405	365
$[\alpha]_{\lambda}^{20}$	+1.00°	+0.75°	+0.85°	+1.15°	+1.20°	+1.37°

Elemental analysis (%):

	C	H	N	
calcd.	57.76	6.25	8.69	
found	57.62	6.05	9.05	anhydrous

E) [[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[bis(phenylmethyl)]-L-glutaminate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M solution of 1-deoxy-1-(methylamino)-D-glucitol (87 mL; 87 mmol) was dropped into a suspension of the compound from the previous preparation (16.4 g; 25.5 mmol) in H_2O (350 mL), stirring until complete dissolution. A 0.482 M solution of $GdCl_3$ (52.9 mL; 25.5 mmol) was slowly added, maintaining the pH of the mixture at 6.5 by addition of a 0.5 M solution of 1-deoxy-1-(methylamino)-D-glucitol. After stirring for 1 h

at room temperature the solution was concentrated (2 kPa; final volume 200 mL; pH 6.17). The mixture was loaded onto a column of Amberlite(R) XAD 1600 polystyrene resin (1500 mL) and the column eluted with water followed by 3:7 CH_3CN/H_2O mixture. The fractions containing the complex were combined and, after concentration, the resulting cloudy solution was filtered over Millipore(R) HA-0.22 µm. After adjusting the pH to 6.96 adding a 0.08 M solution of 1-deoxy-1-methylamino-D-glucitol the solution was evaporated to dryness to give the title compound (27.55 g; 23.2 mmol). Yield 91 %.

m.p.: 125°C

HPLC : 99.7% (area %) - Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;
250 x 4 mm column packed by Merck KGaA;
Temperature: 40°C;
Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 270 mL of acetonitrile mixed with 730 mL of water and 2 mL of 0.1 M EDTA. The solution is buffered to pH 6 with H_3PO_4;
Flow rate: 1 mL min^{-1};
Detection (UV): 210 nm;
Injection: 10 µL;
Sample concentration: 1 mg mL^{-1};
Instrumentation: Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA.

Free ligand (0.001 M $GdCl_3$): <0.1%

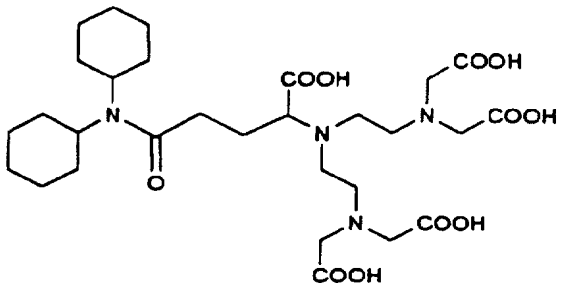
MS spectrum was consistent with the structure.

Elemental analysis (%):

	C	H	N	Gd	
Calcd.	45.44	6.03	7.06	13.22	
Found	45.40	6.16	6.94	13.10	anhydrous

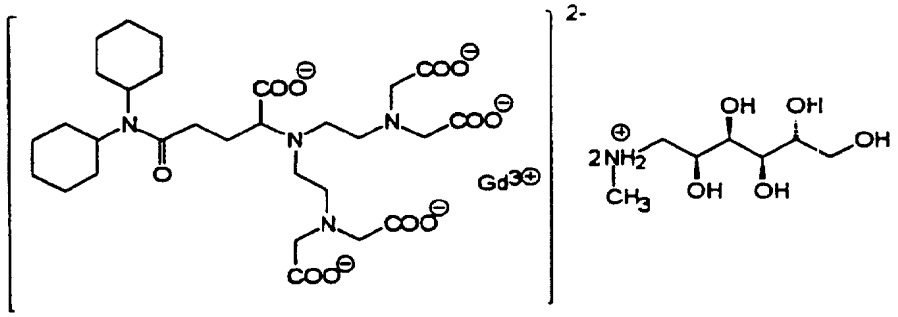
With analogous synthetic method, starting from (S)-5-oxo-3-[(phenylmethoxy)carbonyl]-4-oxazolidinepropanoyl chloride (prepared according to Example 3) and dicyclohexylamine (commercial product), the following ligand and its gadolinium chelate were obtained:

- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[dicyclohexyl]-L-glutamine



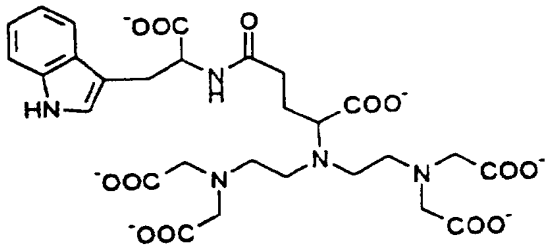
and

- [[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[dicyclohexyl]-L-glutaminato(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)



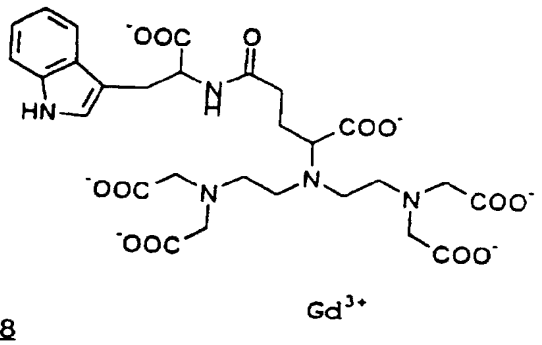
With analogous synthetic method, the following ligand and its gadolinium chelate were obtained:

-[4-carboxy-4-[bis[2-[bis(carboxymethyl)amino]ethyl]-amino]-1-oxobutyl]-L-tryptophane



and

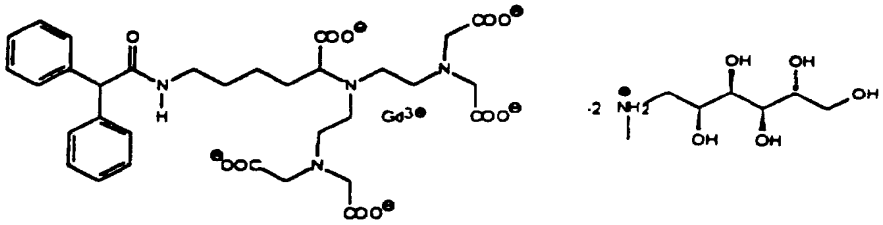
-[[N-[4-carboxy-4-[bis[2-[bis(carboxymethyl)amino]-ethyl]amino]-1-oxobutyl]-L-tryptophanate(6-)]gadolina-te(3-)]trisodium salt



Gd^{3+} Na^{3+}

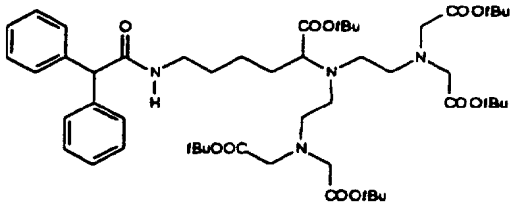
EXAMPLE 8

[[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(di-phenylacetyl)-L-lysinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)



A) N^2,N^2-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]mino]ethyl]-N^6-(diphenylacetyl)-L-lysine 1,1-

dimethylethyl ester



A solution of α-(phenyl)benzeneacetyl chloride (3.46 g; 15 mmol) (commercial product), in $CHCl_3$ (75 mL) was dropped into a solution of N^2,N^2-bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]ethyl]-L-lysine 1,1-dimethylethyl ester, prepared according to Example 2, (11.17 g; 15 mmol) in $CHCl_3$ (190 mL), maintaining the mixture at 5÷10°C. The resulting solution was washed with a saturated aq solution of $NaHCO_3$ (3 x 100 mL); the organic phase was dried over Na_2SO_4 and concentrated to dryness to yield an oil (18 g) which was purified by flash chromatography:

Column: = 100 mm; h = 250 mm

Stationary phase: Silica gel 230-400 mesh Merck KGaA art 9385 (1 kg)

Mobile phase: 7/3 n-hexane/EtOAc

The desired product was obtained (12.2 g; 13 mmol). Yield 87 %.

Acidic titer (0.1 N $HClO_4$) : 104.4%

TLC : Rf 0.21

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 7/3 n-hexane/EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 99.7 % (area %) Chromatographic method:

Stationary phase: Lichrosorb RP-Select B 5 µm;

250 x 4 mm column packed by Merck KGaA;

Temperature: 45°C;

Mobile phase: gradient elution;

A = 0.01 M KH_2PO_4 and 0.017 M H_3PO_4 in water

B = CH_3CN

Gradient timetable:

min	% A	% B
0	95	5
30	20	80
45	20	80

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm, 280 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation : Merck KGaA - Hitachi L 6200 low pressure gradient pump, Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T6300 column thermostat, Merck KGaA - Hitachi L 4000 UV detector.

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

Elemental analysis (%):

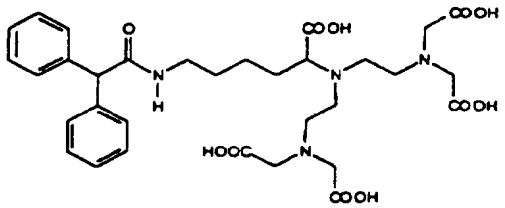
	C	H	N
Calcd.	66.50	8.80	5.97
Found	65.99	8.89	5.76

$[\alpha]^{20}$(c 5.00; $CHCl_3$):

λ (nm)	589	578	546	436	405	365
$[\alpha]_\lambda^{20}$	-22.30°	-24.02°	-27.52°	-49.68°	-41.64°	-86.00°

B) N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(diphenylacetyl)-L-lysine

60



A solution of the pentaester from the previous preparation (10.7 g; 11.4 mmol) in CF_3COOH (150 mL; 1.95 mol) was stirred over 18 h under N_2 atmosphere. After evaporation (40°C; 2 kPa) the residue was dissolved in CH_2Cl_2 (3 x 100 mL) evaporating the solvent each time (40°C; 2 kPa). The crude was dissolved in a 9/1 H_2O/CH_3CN mixture and the solution was loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin. The column was eluted with H_2O (1.5 L), then with 4/1 H_2O/CH_3CN, obtaining the product. After concentration to 120 mL the resulting solution was filtered over Millipore(R) HA 0.45 m and evaporated. The amorphous residue was suspended in CH_3CN and the solvent evaporated. Such procedure was repeated until the desired product was recovered by filtration (5.83 g; 8.9 mmol). Yield 78 %.

mp : 124°C (dec.)

Acidic titer (0.1 N NaOH): 101.1 %

Acidic titer (0.1 N $HClO_4$): 97.4 %

Complexometric titer (0.1 N $GdCl_3$): 96.7 %

TLC : Rf 0.36

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 4/4/2 $CHCl_3/CH_3OH$/25% aq NH_4OH

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 99.9 % (area %) Chromatographic method: the same

of previous Step A)

K.F. : 1.08 %

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

Elemental analysis (%):

	C	H	N	
Calcd.	58.34	6.43	8.51	
Found	57.92	6.45	8.66	anhydrous

$[\alpha]^{20}$(c 2.51; 0.1 M NaOH):

λ (nm)	589	578	546	436	405	365
$[\alpha]_{\lambda}^{20}$	-5.97°	-8.32°	-10.27°	-17.91°	-21.26°	-25.12°

C) [[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(diphenylacetyl)-L-lysinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M aq solution of 1-deoxy-1-methylamino-D-glucitol (17.3 mL; 17.3 mmol) was dropped into a stirred suspension of the free ligand from the previous preparation (3.95 g; 6 mmol) in H_2O (150 mL) to give a clear solution. A 0.4 M solution of $GdCl_3$ (14.5 mL; 5.8 mmol) was slowly added, maintaining the pH of the mixture at 6.5 by addition of a 1 M aq solution of 1-deoxy-1-methylamino-D-glucitol. After stirring for 1 h at room temperature the solution was filtered over Millipore(R) HA 0.45 m and loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (300 mL). The column was eluted with water followed by 9/1 H_2O/CH_3CN mixture. The fractions containing the complex were combined and, after concentration to 150 mL, the

resulting solution was filtered over Millipore(R) HA 0.45 m. The solution was evaporated to dryness to give the title compound (6.2 g; 5.2 mmol). Yield 86 %.

mp : 127°C (dec.)

Free ligand (0.001 M $GdCl_3$) : <0.1 %

HPLC : 99.9% (area %) Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;
250 x 4 mm column packed by Merck KGaA;

Temperature: 40°C;

Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 280 mL of acetonitrile mixed with 720 mL of water and 2 mL of 0.1 M EDTA. The solution is buffered to pH 6 with H_3PO_4;

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation: Merck KGaA - Hitachi L 6200 low pressure gradient pump, Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T6300 column thermostat, Merck KGaA - Hitachi L 4000 UV detector.

K.F. : 2.28 %

MS spectrum was consistent with the structure.

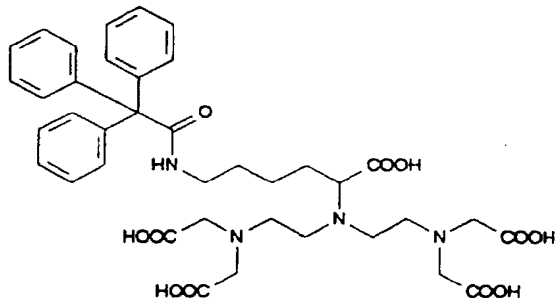
Elemental analysis (%):

	C	H	N	Gd	Cl	
Calcd.	45.91	6.11	6.98	13.07	- -	
Found	46.30	6.24	7.08	13.09	<0.1	anhydrous

With analogous synthetic method, starting from N^2,N^2-bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]-ethyl]-L-lysine 1,1-dimethylethyl ester, prepared

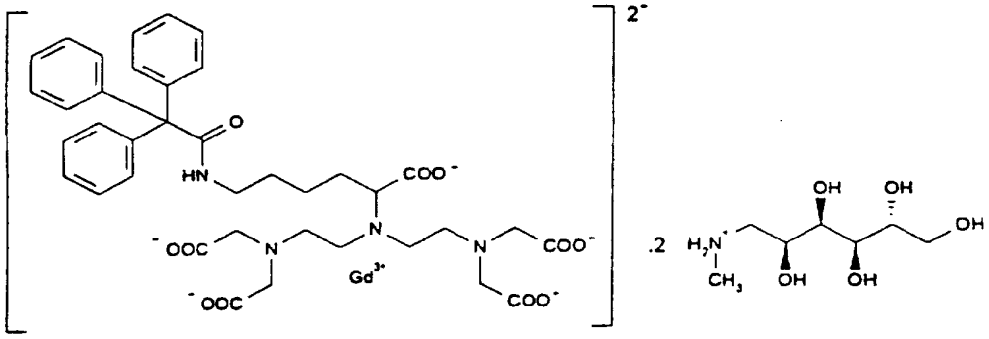
according to Example 2, and, -(diphenyl)benzeneacetyl chloride, prepared from the corresponding commercially available triphenylacetic acid [C.A.S. 595-91-5] with standard procedure, the following ligand and his gadolinium chelate were obtained:

- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(triphenylacetyl)-L-lysine



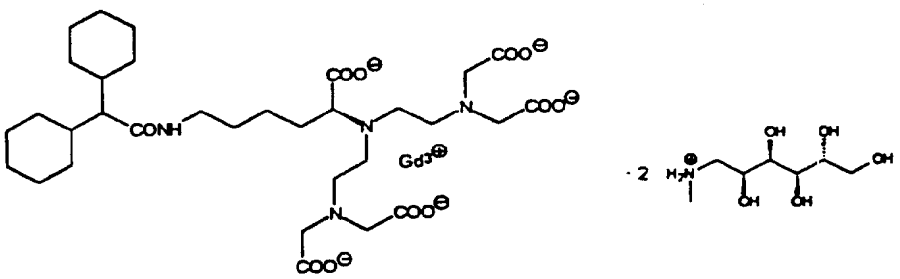
and

- [[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(triphenylacetyl)-L-lysinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2).

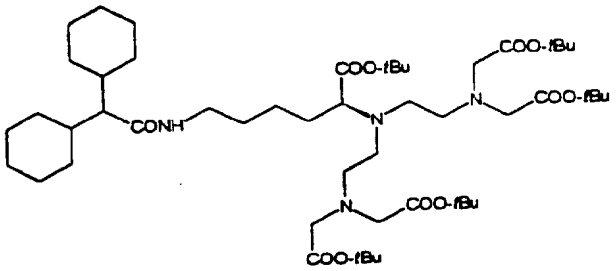


EXAMPLE 9

[[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)



A) N^2,N^2-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysine 1,1-dimethylethyl ester



A solution of α-(cyclohexyl)cyclohexylacetic acid (commercial product) (3.36 g; 15 mmol) in $SOCl_2$ (3.2 mL; 45 mmol) was heated at 40°C for 10 min, then the temperature was increased to 60°C and after 20 min the mixture was heated at reflux for 30 min. The solution was evaporated (40°C; 2 kPa) and the residue was dissolved in CH_2Cl_2 (5 x 4 mL) evaporating the solvent each time. The final residue was dissolved in CH_2Cl_2 (50 mL) and dropped into a solution of N^2,N^2-bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]ethyl]-L-lysine 1,1-dimethylethyl ester, prepared according to Example 2, (11 g; 14.7 mmol) in $CHCl_3$ (150 mL), maintaining the mixture at 5÷10°C. The resulting solution was washed with a saturated aqueous solution of $NaHCO_3$ (3 x 50 mL); the organic phase was dried over Na_2SO_4 and concentrated to dryness to yield an oil

(20 g) which was purified by flash chromatography:

Column: 60 mm; h = 350 mm

Stationary phase: Silica gel 230-400 mesh Merck KGaA art 9385 (0.5 kg)

Mobile phase: 7/3 n-hexane/EtOAc.

The desired product was obtained (11.3 g; 11.9 mmol). Yield 79%.

Acidic titer (0.1 N $HClO_4$) : 95%

TLC : Rf 0.39

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 8/2 n-hexane/EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

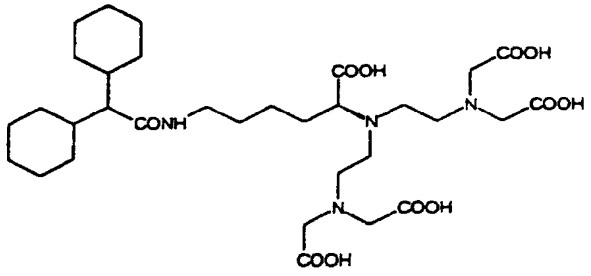
^{13}C-NMR, ^{1}H-NMR and MS spectra were consistent with the structure.

Weight loss : (80°C) 3.81 %

Elemental analysis (%):

	C	H	N
Calcd.	65.65	9.96	5.89
Found	65.73	10.09	5.78

B) N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysine



A solution of the pentaester from the previous preparation (9 g; 9.4 mmol) in CF_3COOH (110 mL;

1.44 mol) was stirred over 40 h under N_2 atmosphere. After evaporation (40°C; 2 kPa) the residue was dissolved in CH_2Cl_2 (5 x 100 mL) evaporating the solvent each time (40°C; 2 kPa). The crude was dissolved in a 9/1 H_2O/CH_3CN mixture and the solution was loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (300 mL). The column was eluted at first with H_2O (1.5 L) then elution with 4/1 H_2O/CH_3CN (1.5 L) afforded the product. After concentration to 300 mL the resulting solution was filtered over Millipore HA 0.45 m and concentrated to the final volume of 100 mL. After 1 h at 20°C the precipitate was filtered and dried (40°C; 2 kPa; P_2O_5) to yield the desired product (3.05 g; 4.5 mmol). Yield 48 %.

mp : 145°C (dec.)

Acidic titer (0.1 N NaOH) : 95 %

Complexometric titer (0.001 N $GdCl_3$) : 96.3 %

HPLC : 99.2 % (area %) - Chromatographic method:

Stationary phase: Lichrosorb RP-Select B 5 (?)m;

250 x 4 mm column packed by Merck KGaA;

Temperature: 45°C;

Mobile phase: gradient elution;

A = 0.017 M H_3PO_4 in water

B = CH_3CN

Gradient timetable:

min	% A	% B
0	95	5
5	95	5
30	20	80
45	20	80

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 10 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation : Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector.

K.F. : 2.09 %

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

Elemental analysis (%):

	C	H	N	F	
Calcd.	57.30	8.11	8.35	- -	
Found	57.58	8.20	8.35	< 0.1	anhydrous

$[\alpha]^{20}$(c 2.5; 0.1 M NaOH)

λ (nm)	589	578	546	436	405	365
$[\alpha]_{\lambda}^{20}$	-9.80°	-11.48°	-13.44°	-20.72°	-24.12°	-29.80°

C) [[N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysinate(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-methylamino-D-glucitol (1:2)

A 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol (9.5 mL; 9.5 mmol) was dropped into a stirred suspension of the free ligand from the previous preparation (2.23 g; 3.3 mmol) in H_2O (50 mL) to give a clear solution. A 0.1 M solution of $GdCl_3$ (32.5 mL; 3.25 mmol) was slowly added, maintaining the pH of the mixture at 5.5 by addition of a 1 M aqueous solution of 1-deoxy-1-methylamino-D-glucitol. After stirring for 1 h

at room temperature the solution was filtered over Millipore(R) HA 0.45 m and loaded onto a column of Amberlite(R) XAD 16-00 polystyrene resin (200 mL). The column was eluted with water (300 mL) followed by 3/1 H_2O/CH_3CN mixture. The fractions containing the complex were combined and, after concentration to 150 mL, the resulting cloudy solution was filtered over Millipore(R) HA 0.45 m. The solution was evaporated to 20 mL and the pH was corrected from 8.5 to 7 with 0.1 M HCl (0.6 mL). The resulting solution was evaporated to dryness to give the title compound (3.6 g; 3 mmol). Yield 91 %.

mp : 152°C (dec.)

Free ligand (0.001 M $GdCl_3$) : <0.1 %

HPLC : 99.5% (area %) - Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;
250 x 4 mm column packed by Merck KGaA;
Temperature: 40°C;
Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 400 mL of acetonitrile mixed with 600 mL of water. The solution is buffered to pH 6 with H_3PO_4;
Flow rate: 1 mL min^{-1};
Detection (UV): 210 nm;
Injection: 10 µL;
Sample concentration: 1 mg mL^{-1};
Instrumentation: Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector.

K.F. : 2.46 %

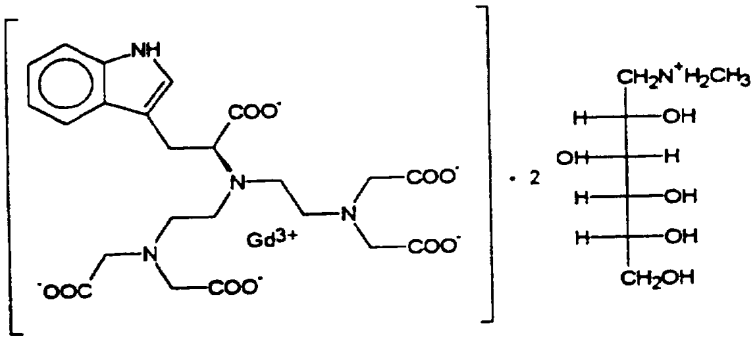
MS and IR spectra were consistent with the structure.

Elemental analysis (%):

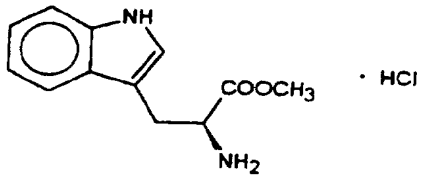
	C	H	Gd	N
Calcd.	45.46	7.05	12.94	6.91
Found	45.32	7.16	12.60	6.81

EXAMPLE 10

[[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-tryptophanate(5-)] gadolinate(2-)] dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)



A) L-Tryptophan methyl ester hydrochloride



A 1.2 M solution of HCl in MeOH (440 mL; 0.528 mol) was added to a suspension of L-tryptophan (commercial product) (30.6 g; 150 mmol) in MeOH (70 mL). The resulting clear solution was stirred for 5 days at 20°C. The solution was concentrated (35°C; 1.3 kPa) to yield a solid which was dissolved in MeOH (10 mL). Et_2O (300 mL) was added to the solution and the mixture was vigorously stirred for 1 h. The mixture was filtered and the solid

was washed with Et_2O (70 mL). The combined solutions were concentrated (35°C; 1.3 kPa) to a volume of 100 mL and filtered. The solid materials were combined and dried (40°C; P_2O_5; 1.3 kPa) to give as a white solid the desired product (38.5 g; 149.5 mmol). Quantitative yield.

mp : 211°C dec.

Argentometric titer (0.1 M $AgNO_3$) : 102 %

HPLC : 99.7 % (area %) Chromatographic method: the same of Ex. 4, Step A)

TLC : Rf 0.38

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 9:1 CH_2Cl_2:MeOH

Detection: 1% $KMnO_4$ in 1 M NaOH

^{13}C-NMR, ^1H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$(c 2.2; CH_3OH):

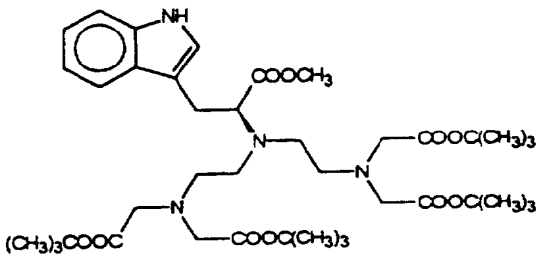
λ(nm)	589	578	546	436	405
$[\alpha]_\lambda^{20}$	+ 17.9°	+ 18.91°	+ 22.01°	+ 45.03°	+ 59.27°

Elemental analysis (%):

	C	H	N	Cl
Calcd.	56.58	5.94	11.00	13.92
Found	56.71	5.97	11.08	13.75

B) N,N-Bis[2-[bis[2-(1,1-dimethylethoxy)-2-oxo-ethyl]amino]ethyl]-L-tryptophan methyl ester

71



A suspension of L-Tryptophan methyl ester hydrochloride (12.9 g; 50 mmol) in CH_2Cl_2 (150 mL) was washed with a saturated aq. solution of $NaHCO_3$ until basic pH of the aqueous phase. After separation the organic phase was dried (Na_2SO_4) and concentrated (35°C; 1.3 kPa) to yield an oil, that was dissolved in CH_3CN (500 mL). N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester, prepared according to Example 1, (17.6 g; 50 mmol) and 2 M pH 7 phosphate buffer (500 mL) were then added. The mixture was vigorously stirred for 3 h, then N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (16.7 g; 47 mmol) was added and the mixture was stirred for 16 h. After further addition of N-(2-bromoethyl)-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]glycine 1,1-dimethylethyl ester (3.5 g; 10 mmol) and stirring for 3h the reaction was stopped. The phases were separated and the organic phase was evaporated to dryness (35°C; 1.3 kPa). The residue was suspended in Et_2O (500 mL) and washed with brine (2x100 mL) and with H_2O (50 mL). The organic phase was dried (Na_2SO_4) and evaporated to yield an oil (39.8 g), which was purified by flash chromatography:

Silica gel column

Stationary phase: Silica gel 230-400 mesh Merck

KGaA art 9385 (1 kg)

Mobile phase: 7:3 n-hexane: EtOAc (10 L)).

The desired product was obtained (6.22 g; 34.4 mmol).

Yield 69 %

mp : 71°C

Acidic titer (0.1 M $HClO_4$) : 97.4 %

TLC : Rf 0.44

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 6:4 n-hexane:EtOAc

Detection: 1% $KMnO_4$ in 1 M NaOH

HPLC : 99.3 % (area %) Chromatographic method: the same of Ex. 4, Step A)

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

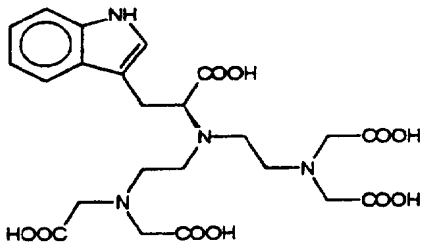
$[\alpha]^{20}$(c 2.2; $CHCl_3$):

$\lambda_{(nm)}$	589	578	546	436	405
$[\alpha]_{\lambda}^{20}$	-17.86°	-18.50°	-21.12°	-38.35°	-47.78°

Elemental analysis (%):

	C	H	N
Calcd.	63.13	8.48	7.36
Found	63.11	8.59	7.10

C) N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-tryptophan



A 0.5 M solution of H_2SO_4 (162 mL; 81 mmol) was added to a suspension of the pentaester from the previous preparation (24 g; 31.5 mmol) in H_2O (160 mL) over 15 min. The mixture was stirred at 90°C for 2.5 h. The resulting clear solution was cooled and the pH was adjusted to 13.5 by adding 6 M NaOH. The mixture was stirred at 20°C for 16 h. The pH was adjusted to 1.5 by adding 2 M HCl and the solution loaded onto a column of Amberlite(R) XAD 1600 polystyrene resin (1 L). Elution with 9:1 H_2O/CH_3CN afforded the free ligand (13.3 g; 25.4 mmol). Yield 80 %.

mp : 142°C (dec.)

Acidic titer (0.1 M NaOH) : 103.2 %

Acidic titer (0.1 M $HClO_4$) : 102.9 %

Complexometric titer (0.1 M $ZnSO_4$) : 103 %

Complexometric titer (0.001 M $GdCl_3$) : 103 %

HPLC: 98.8% (area %) Chromatographic method: the same of Ex. 4, Step A)

TLC : Rf 0.08

Stationary phase: Silica gel plates 60 F_{254} Merck KGaA art 5715

Mobile phase: 6:3:1 $CHCl_3$:MeOH:25% aq. NH_4OH

Detection: 1% $KMnO_4$ in 1 M NaOH

K.F. : 4.16%

^{13}C-NMR, ^{1}H-NMR, MS and IR spectra were consistent with the structure.

$[\alpha]^{20}$(c 2.6; 0.02 N NaOH):

λ(nm)	589	578	546	436
$[\alpha]_\lambda^{20}$	-13.34°	-14.07°	-16.18°	-26.92°

Elemental analysis (%):

	C	H	N	
Calcd.	52.87	5.79	10.72	
Found	53.09	5.94	10.71	anhydrous

D) [[N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-tryptophanate-(5-)]gadolinate(2-)] dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

A mixture of the free ligand from the previous preparation (9.4 g; 17.5 mmol), Gd_2O_3 (3.17 g; 8.77 mmol) and 1.01 M 1-deoxy-1-(methylamino)-D-glucitol (31.62 mL; 32 mmol) in H_2O (970 mL) was stirred for 16 h at 50°C. The mixture was filtered over Millipore(R) (HAWP 0.45 m) and loaded onto a column of Amberlite(R) XAD-1600 polystyrene resin (1 L). The product was obtained by elution with 95:5 H_2O:CH_3CN. The eluate was concentrated to 1 L and, after adjusting the pH to 7 with a 1 M 1-deoxy-1-(methylamino)-D-glucitol solution, was evaporated to dryness (1.3 kPa; 40° C; P_2O_5) to yield the title compound (18.1 g; 17 mmol). Yield 97%.

mp : 148°C (dec.)

Free ligand (0.001 M $GdCl_3$) : < 0.1 %

HPLC : 98.6 % (area %) Chromatographic method:

Stationary phase: Lichrospher 100 RP-8 5 µm;

250 x 4 mm column packed by Merck KGaA;

Temperature: 40°C;

Mobile phase: isocratic elution with premixed mobile phase: 1 g of n-octylamine is added to 270 mL of acetonitrile mixed with 730 mL of water. The solution is buffered to pH 6 with H_3PO_4;

Flow rate: 1 mL min^{-1};

Detection (UV): 210 nm;

Injection: 5 µL;

Sample concentration: 1 mg mL^{-1};

Instrumentation: Merck KGaA - Hitachi high pressure gradient pump system (L6200 and L6000), Merck KGaA - Hitachi AS 2000 autosampler, Merck KGaA T 6300 column thermostat, Merck KGaA - Hitachi L 4500 diode array detector, Merck KGaA.

K.F. : 3.66 %

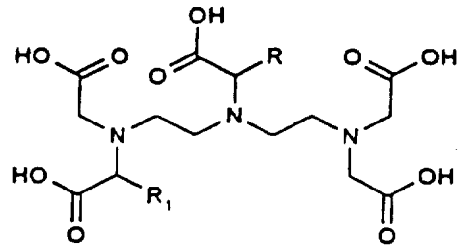
MS spectrum was consistent with the structure.

Elemental analysis (%):

	C	H	Gd	N	O	
Calcd.	41.64	5.76	14.74	7.87	29.98	
Found	41.98	5.90	14.63	7.82	29.30	anhydrous

CLAIMS

1. Compounds of general formula (I), both in the racemic and optically active forms



(I)

in which :

R is H, or a linear or branched, saturated or unsaturated C_1-C_{20} alkyl, optionally interrupted by one or more -CH(OH)-, -CONH-, -NHCO-, -CO-, -CH(NH_2)-, -SO-, -SO_2-, SO_2NH- groups and/or one or more N, O, S atoms, optionally substituted with one or more -COOH groups and/or amide or ester derivatives thereof, and in which said alkyl chain is interrupted or substituted by at least 2, which are independently the same or different, isolated or fused, cyclic L residues, with the proviso that, when some L residues are fused together, the resulting polycyclic unit comprises no more than 3 cyclic group, and in which

L is a carbocyclic or heterocyclic, saturated or unsaturated or aromatic cyclic unit, comprising from 5 to 6 atoms, optionally substituted by one or more X groups, which are independently the same or different, in which

X is OH, halogen, NH_2, NHZ, $N(Z)_2$, -OZ- , -SZ-, COZ, where the Z groups can independently be a

C_1-C_5 linear or branched alkyl, optionally substituted with one or more -OH, -COOH or alkoxy groups,

or said X group is a -COOH group or a derivative thereof, such as an ester or an amido group, or an -SOZH group or an amido derivative of the same;

R_1 is the same as R with the provisos that:

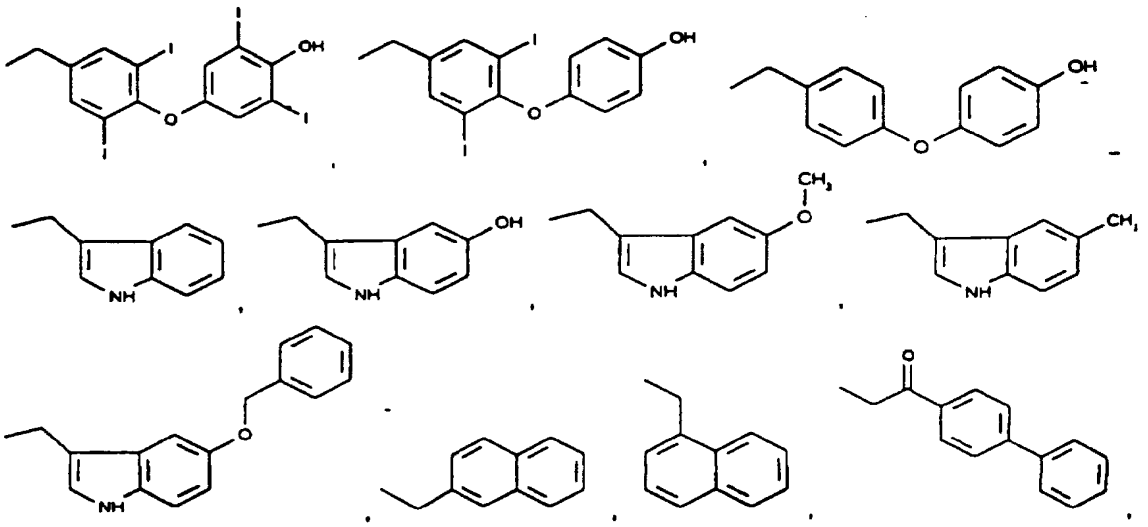
R and R_1 cannot be at the same time H;

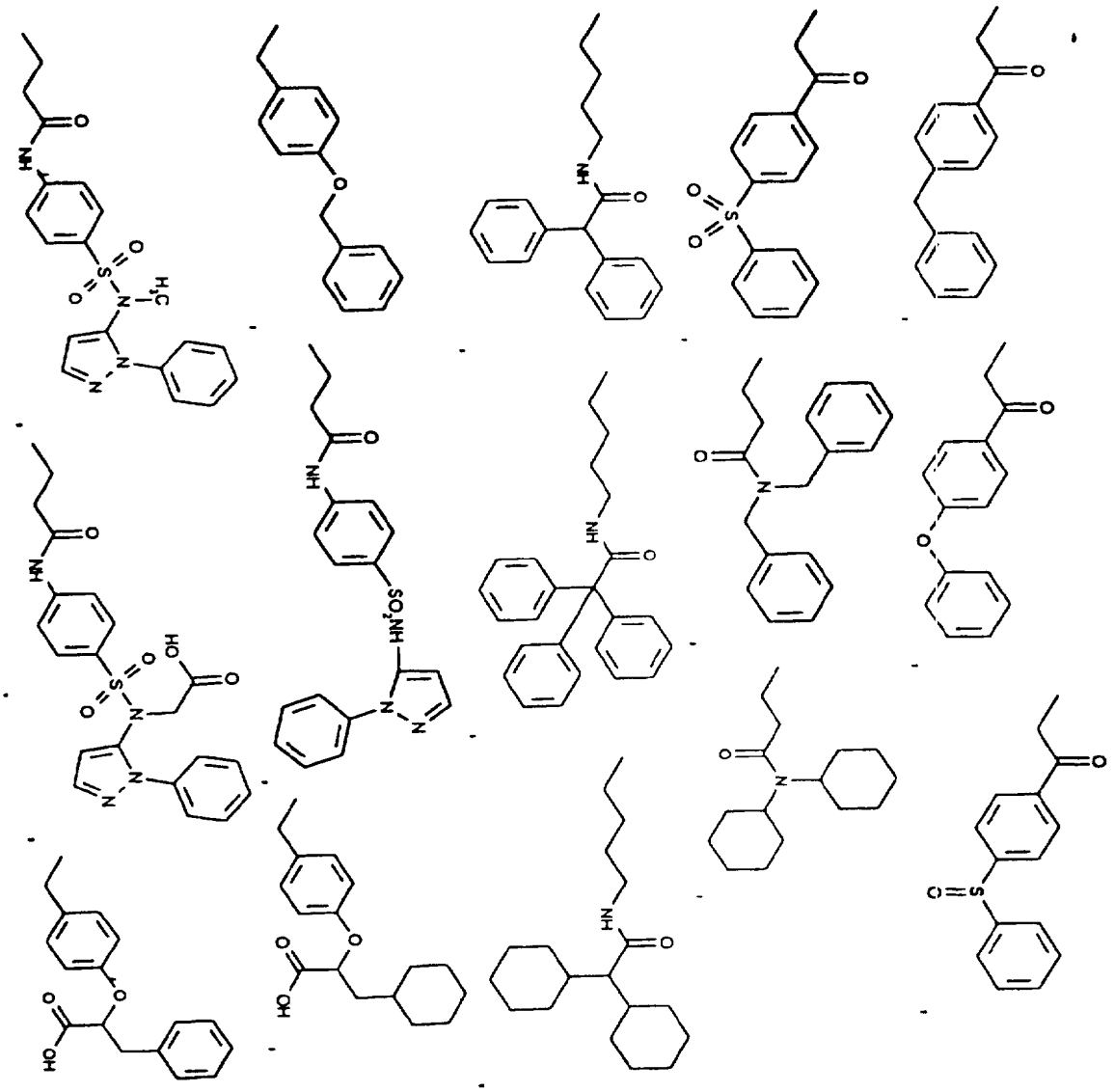
when R is different from H, R_1 is H;

when R_1 is different from H, R is H;

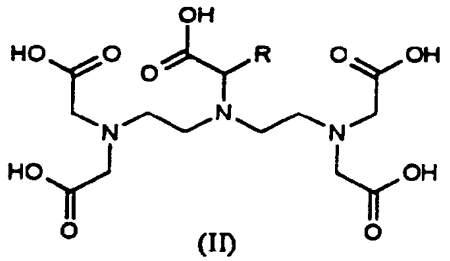
as well as the complexes of the compounds of formula (I) with metal ions of atomic number from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83 and the salts thereof with physiologically acceptable organic bases selected from primary, secondary or tertiary amines, or basic amino acids, or with inorganic bases the cations of which are sodium, potassium, magnesium, calcium or the mixtures thereof.

2. Compounds as claimed in claim 1, wherein R or R_1 are selected from the following groups:





3. Compounds as claimed in claim 1, of general formula (II), both in the racemic and optically active forms,



(II)

in which R has the same meanings as in claim 1, but is different from H,

as well as the complexes of the compounds of formula (II) with metal ions of atomic number from 20 to 31, 39, from 42 to 44, 49 and from 57 to 83 and the salts thereof with physiologically acceptable organic bases selected from primary, secondary or tertiary amines, or basic amino acids, or with inorganic bases the cations of which are sodium, potassium, magnesium, calcium or the mixtures thereof.

4. Compounds as claimed in claims 1 to 3, wherein the complexed bi- or trivalent metal ion is selected from $Fe^{(2+)}$, $Fe^{(3+)}$, $Cu^{(2+)}$, $Cr^{(3+)}$, $Gd^{(3+)}$, $Eu^{(3+)}$, $Dy^{(3+)}$, $La^{(3+)}$, $Yb^{(3+)}$ and $Mn^{(2+)}$.

5. Compounds as claimed in claims 1 to 3, selected from the group consisting of:

- N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine;
- N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-L-tyrosine;
- N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-O-(3,5-diiodo-4-hydroxyphenyl)-3,5-diiodo-L-tyrosine;

- N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-O-(3-iodo-4-hydroxypenyl)-3,5-diiodo-L-tyrosine;
- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[bis(phenylmethyl)]-L-glutamine;
- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[dicyclohexyl]-L-glutamine;
- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(diphenylacetyl)-L-lysine;
- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(triphenylacetyl)-L-lysine;
- N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysine;
- [N-[4-carboxy-4-[bis[2-[bis(carboxymethyl)-amino]ethyl]amino]-1-oxobutyl]-L-tryptophane;
- [[N,N-bis[-2-[bis(carboxymethyl)amino]ethyl]-L-tryptophane.

6. A paramagnetic chelate as claimed in claim 3, selected from the following group:

- gadolinium complex of N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-3,5-diiodo-L-tyrosine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);
- gadolinium complex of N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-O-(4-hydroxyphenyl)-L-tyrosine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);
- gadolinium complex of N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-O-(3,5-diiodo-4-hydroxyphenyl)-3,5-diiodo-L-tyrosine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);
- gadolinium complex of N,N-bis[2-[bis-(carboxymethyl)aminoethyl]-O-(3-iodo-4-hydroxyphenyl)-

3,5-diiodo-L-tyrosine;

- gadolinium complex of N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[bis(phenylmethyl)]-L-glutamine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

- gadolinium complex of N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N,N-[dicyclohexyl]-L-glutamine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

- gadolinium complex of [N-[4-carboxy-4-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]-1-oxobutyl]-L-tryptophane salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

- gadolinium complex of N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(diphenylacetyl)-L-lysine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

- gadolinium complex of N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(triphenylacetyl)-L-lysine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

- gadolinium complex of N^2,N^2-Bis[2-[bis(carboxymethyl)amino]ethyl]-N^6-(dicyclohexylacetyl)-L-lysine salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2).

- gadolinium complex of [[N,N-bis[-2-[bis(carboxymethyl)amino]ethyl]-L-tryptophane salified with 1-deoxy-1-(methylamino)-D-glucitol (1:2);

7. Compounds as claimed in claims 1 to 6, further characterized in that the relaxivity values (r_1, r_2) in human serum reconstructed with Seronorm™ Human, at a concentration comprised from 0 to 1 mM, at 20 MHz and 39°C, is higher or the same as 15 $s^{-1}mM^{-1}$.

8. A contrast diagnostic pharmaceutical composition for Magnetic Resonance Imaging comprising at least one of the complex chelates as claimed in claims 1 to 6 or a physiologically acceptable salt thereof.

9. A pharmaceutical composition as claimed in claim 8, for imaging of human or animal body organs and/or tissues, by use of Nuclear Magnetic Resonance.

10. The use of the complex chelates of the compounds as claimed in claims 1 to 6, or of the salts thereof, for the preparation of diagnostic formulations for M.R.I., for obtaining images of human or animal body organs and/or tissues by use of Nuclear Magnetic Resonance.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/03997

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/36 C07C229/22 A61K49/00 C07D209/20 C07C237/06
C07C237/04 C07C233/48 C07C233/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 514 810 A (PLATZEK JOHANNES ET AL) 7 May 1996 see column 2, line 39 - column 3, line 18 ---	1-10
A	DE 43 41 724 A (SCHERING AG) 8 June 1995 see examples 11,12 see claims -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 1997	18. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
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